```
=> d his

     (FILE 'HOME' ENTERED AT 11:21:12 ON 11 MAR 2002)

     FILE 'HCAPLUS' ENTERED AT 11:22:20 ON 11 MAR 2002
L1        452095 S GLASS? OR SILICATE#
L2         10849 S DRY### (L) (FREEZ? OR VACUUM OR SPRAY? OR CHILL?)
L3         57308 S DRYING
L4          1711 S L1 AND (L3 OR L2)
L5        339215 S STABILI?
L6            81 S L4 AND L5
L7            14 S AMORPHUS?
L8        100140 S AMORPHOUS
L9             8 S L8 AND L6
L10          264 S DRIED AND L1
L11           40 S L10 AND L5
L12           94 S L11 OR L6
L13           10 S L12 AND L8

     FILE 'REGISTRY' ENTERED AT 11:26:26 ON 11 MAR 2002
L14            2 S MANNITOL/CN
                 E GALACTITOL/CN
L15            1 S E3
                 E XYLITOL/CN
L16            1 S E3
                 E ARABINITOL/CN
L17            1 S E3
                 E INOSITOL/CN
L18            2 S E3
L19            7 S L14-L18

     FILE 'HCAPLUS' ENTERED AT 11:28:16 ON 11 MAR 2002
L20        37900 S L19 OR MANNITOL# OR GALACTITOL# OR XYLITOL# OR ARABINITOL# OR
L21         2724 S SUGAR (L) ALC?
L22         2664 S ALDITOL#
                 E ALDITOL/CT
                 E E8+ALL
L23        41220 S L20 OR L21 OR L22
L24           10 S L23 AND L12
L25         1865 S L4 OR L10
L26           38 S L23 AND L25
L27           14 S L26 AND (STABIL?/AB OR FACILITA?/AB OR FACILITAT OR L5)
L28            0 S L26 AND FACILITAT?
L29           14 S L27 OR L24
L30           22 S L13 OR L29
```

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=> fil reg
FILE 'REGISTRY' ENTERED AT 11:34:12 ON 11 MAR 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 American Chemical Society (ACS)

STRUCTURE FILE UPDATES:     8 MAR 2002  HIGHEST RN 400002-69-9
DICTIONARY FILE UPDATES:    8 MAR 2002  HIGHEST RN 400002-69-9

TSCA INFORMATION NOW CURRENT THROUGH July 7, 2001

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Calculated physical property data is now available.  See HELP PROPERTIES
for more information.  See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

The P indicator for Preparations was not generated for all of the
CAS Registry Numbers that were added to the H/Z/CA/CAplus files between
12/27/01 and 1/23/02.  Use of the P indicator in online and SDI searches
during this period, either directly appended to a CAS Registry Number
or by qualifying an L-number with /P, may have yielded incomplete results.
As of 1/23/02, the situation has been resolved.  Also, note that searches
conducted using the PREP role indicator were not affected.

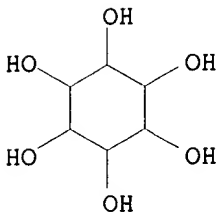
Customers running searches and/or SDIs in the H/Z/CA/CAplus files
incorporating CAS Registry Numbers with the P indicator between 12/27/01
and 1/23/02, are encouraged to re-run these strategies.  Contact the
CAS Help Desk at 1-800-848-6533 in North America or 1-614-447-3698,
worldwide, or send an e-mail to help@cas.org for further assistance or to
receive a credit for any duplicate searches.

=> d que l19
L14             2 SEA FILE=REGISTRY ABB=ON  MANNITOL/CN
L15             1 SEA FILE=REGISTRY ABB=ON  GALACTITOL/CN
L16             1 SEA FILE=REGISTRY ABB=ON  XYLITOL/CN
L17             1 SEA FILE=REGISTRY ABB=ON  ARABINITOL/CN
L18             2 SEA FILE=REGISTRY ABB=ON  INOSITOL/CN
L19             7 SEA FILE=REGISTRY ABB=ON  (L14 OR L15 OR L16 OR L17 OR L18)


=> d l19 1-7

L19  ANSWER 1 OF 7  REGISTRY  COPYRIGHT 2002 ACS
RN   6917-35-7  REGISTRY
CN   Inositol (8CI, 9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   1,2,3,4,5,6-Cyclohexanehexol
CN   Inosite
FS   3D CONCORD
DR   173524-45-3
MF   C6 H12 O6
CI   COM
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS,
       BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS,
```

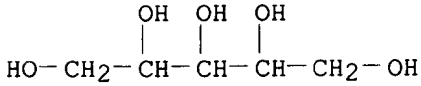
CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, MEDLINE, NIOSHTIC, PIRA, PROMT, SPECINFO, TOXCENTER, TULSA, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

123 REFERENCES IN FILE CA (1967 TO DATE)
20 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
124 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L19 ANSWER 2 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 2152-56-9 REGISTRY
CN **Arabinitol (8CI, 9CI)** (CA INDEX NAME)
OTHER NAMES:
CN (.+-.)-Arabitol
CN Arabite
CN Arabitol
CN DL-Arabitol
CN Lyxitol
DR 6018-27-5
MF C5 H12 O5
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, EMBASE, GMELIN*, HODOC*, IFICDB, IFIPAT, IFIUDB, MEDLINE, MRCK*, NAPRALERT, NIOSHTIC, PROMT, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

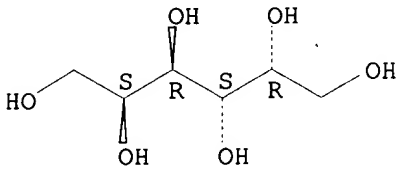


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

645 REFERENCES IN FILE CA (1967 TO DATE)
23 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
645 REFERENCES IN FILE CAPLUS (1967 TO DATE)
5 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L19 ANSWER 3 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 608-66-2 REGISTRY
CN **Galactitol (6CI, 8CI, 9CI)** (CA INDEX NAME)
OTHER NAMES:
CN Dulcite
CN Dulcitol
CN Dulcose
CN Euonymit
CN Melampyrin
CN Melampyrit
FS STEREOSEARCH
DR 18089-21-9, 40742-76-5, 362631-40-1
MF C6 H14 O6
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CHEMLIST, CSCHEM, DDFU, DETHERM*, DRUGU, EMBASE, GMELIN*, HODOC*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, PROMT, SPECINFO, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

Relative stereochemistry.

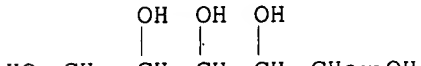


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1117 REFERENCES IN FILE CA (1967 TO DATE)
53 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1117 REFERENCES IN FILE CAPLUS (1967 TO DATE)
59 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L19 ANSWER 4 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 87-99-0 REGISTRY
CN **Xylitol (6CI, 8CI, 9CI)** (CA INDEX NAME)
OTHER NAMES:
CN Klinit
CN Kylit
CN Wood sugar alcohol
CN Xylisorb
CN Xylite
CN Xylite (sugar)
CN Xylitol C
CN Xylitol CM 90
CN Xyliton
DR 12426-00-5, 7313-55-5, 16277-71-7, 37191-59-6, 75398-81-1, 84709-42-2
MF C5 H12 O5
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DETHERM*, DRUGU,

EMBASE, GMELIN*, HODOC*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PIRA, PROMT, RTECS*, SPECINFO, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



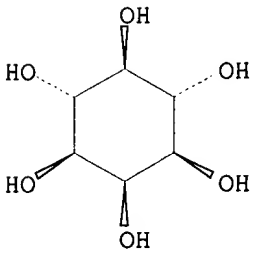
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4026 REFERENCES IN FILE CA (1967 TO DATE)
142 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
4032 REFERENCES IN FILE CAPLUS (1967 TO DATE)
77 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L19 ANSWER 5 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 87-89-8 REGISTRY
CN myo-Inositol (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Inositol, myo- (8CI)
OTHER NAMES:
CN cis-1,2,3,5-trans-4,6-Cyclohexanehexol
CN Dambose
CN i-Inositol
CN i-Inositol
CN Inosital
CN Inositene
CN Inositina
CN **Inositol**
CN Iso-inositol
CN iso-Inositol
CN Meat sugar
CN meso-Inositol
CN Mesoinosit
CN Mesoinosite
CN Mesoinositol
CN Mesol
CN Mesovit
CN MI
CN Myoinosite
CN Myoinositol
CN Nucite
CN Phaseomannite
CN Phaseomannitol
CN Scyllite
FS STEREOSEARCH
DR 53319-35-0
MF C6 H12 O6
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DETHERM*, DIOGENES, DIPPR*, DRUGU, EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PIRA, PROMT, RTECS*, SPECINFO, TOXCENTER,

TULSA, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

Relative stereochemistry.

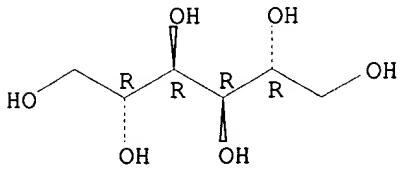


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5745 REFERENCES IN FILE CA (1967 TO DATE)
479 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
5753 REFERENCES IN FILE CAPLUS (1967 TO DATE)
9 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L19 ANSWER 6 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 87-78-5 REGISTRY
CN **Mannitol (8CI, 9CI)** (CA INDEX NAME)
OTHER NAMES:
CN Mannidex 16700
FS STEREOSEARCH
DR 133-43-7, 36413-61-3, 5149-40-6
MF C6 H14 O6
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMINFORMRX, CHEMLIST, CIN, DETHERM*, DIOGENES, EMBASE, GMELIN*, HODOC*, IFICDB, IFIPAT, IFIUDB, MEDLINE, NAPRALERT, NIOSHTIC, PDLCOM*, PHARMASEARCH, PIRA, PROMT, RTECS*, TOXCENTER, TULSA, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

Relative stereochemistry.



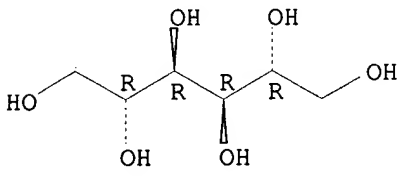
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

115 REFERENCES IN FILE CA (1967 TO DATE)
13 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
117 REFERENCES IN FILE CAPLUS (1967 TO DATE)

1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L19 ANSWER 7 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 69-65-8 REGISTRY
CN D-Mannitol (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Cordycepic acid (6CI, 7CI)
CN Mannitol, D- (8CI)
OTHER NAMES:
CN D-(-)-Mannitol
CN Diosmol
CN Isotol
CN Maniton S
CN Manna sugar
CN Mannidex
CN Mannigen
CN Mannistol
CN Mannit
CN Mannite
CN **Mannitol**
CN Mannitolum
CN Mannogem 2080
CN Marine Crystal
CN Osmitrol
CN Osmosal
FS STEREOSEARCH
DR 123897-58-5, 75398-80-0, 85085-15-0
MF C6 H14 O6
CI COM
LC STN Files: ADISNEWS, AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DRUGU, EMBASE, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PDLCOM*, PHARMASEARCH, PIRA, PROMT, RTECS*, SPECINFO, TOXCENTER, TULSA, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

10986 REFERENCES IN FILE CA (1967 TO DATE)
259 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
11001 REFERENCES IN FILE CAPLUS (1967 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 11:34:33 ON 11 MAR 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 11 Mar 2002 VOL 136 ISS 11
FILE LAST UPDATED: 10 Mar 2002 (20020310/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

The P indicator for Preparations was not generated for all of the CAS Registry Numbers that were added to the CAS files between 12/27/01 and 1/23/02. As of 1/23/02, the situation has been resolved. Searches and/or SDIs in the H/Z/CA/CAplus files incorporating CAS Registry Numbers with the P indicator executed between 12/27/01 and 1/23/02 may be incomplete. See the NEWS message on this topic for more information.
'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> d his l1-l13;d his l20-

(FILE 'HOME' ENTERED AT 11:21:12 ON 11 MAR 2002)

FILE 'HCAPLUS' ENTERED AT 11:22:20 ON 11 MAR 2002
L1 452095 S GLASS? OR SILICATE#
L2 10849 S DRY### (L) (FREEZ? OR VACUUM OR SPRAY? OR CHILL?)
L3 57308 S DRYING
L4 1711 S L1 AND (L3 OR L2)
L5 339215 S STABILI?
L6 81 S L4 AND L5
L7 14 S AMORPHUS?
L8 100140 S AMORPHOUS
L9 8 S L8 AND L6
L10 264 S DRIED AND L1
L11 40 S L10 AND L5
L12 94 S L11 OR L6
L13 10 S L12 AND L8 ← ignore highlighting

(FILE 'HCAPLUS' ENTERED AT 11:28:16 ON 11 MAR 2002)
L20 37900 S L19 OR MANNITOL# OR GALACTITOL# OR XYLITOL# OR ARABINITOL# OR
L21 2724 S SUGAR (L) ALC?

```
L22         2664 S ALDITOL#
                 E ALDITOL/CT
                 E E8+ALL
L23        41220 S L20 OR L21 OR L22
L24           10 S L23 AND L12
L25         1865 S L4 OR L10
L26           38 S L23 AND L25
L27           14 S L26 AND (STABIL?/AB OR FACILITA?/AB OR FACILITAT OR L5)
L28            0 S L26 AND FACILITAT?
L29           14 S L27 OR L24
L30           22 S L13 OR L29

     FILE 'REGISTRY' ENTERED AT 11:34:12 ON 11 MAR 2002

     FILE 'HCAPLUS' ENTERED AT 11:34:33 ON 11 MAR 2002

=> d .ca l30 1-22

L30  ANSWER 1 OF 22  HCAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2001:888748  HCAPLUS
DOCUMENT NUMBER:          136:133793
TITLE:                    A DSC study of hydrated sugar
                          alcohols: isomalt
AUTHOR(S):                Borde, B.; Cesaro, A.
CORPORATE SOURCE:         Dep. of Biochemistry, Biophysics and Macromolecular
                          Chemistry, University of Trieste, Trieste, I-34127,
                          Italy
SOURCE:                   Journal of Thermal Analysis and Calorimetry (2001),
                          66(1), 179-195
                          CODEN: JTACF7; ISSN: 1418-2874
PUBLISHER:                Kluwer Academic Publishers
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   A DSC study was carried out on isomalt, a com. sugar alc. derived from
     sucrose and widely used as a sweetener in the food industry.  Isomalt is a
     mixt. of two isomers: .alpha.-D-glucopyranosyl-1-6-mannitol and
     .alpha.-D-glucopyranosyl-1-6-sorbitol.  Release of the water of crystn.
     (around 100.degree.C) and melting (around 150.degree.C) were phenomenol.
     characterized using different scanning rates and heat treatments.  The
     effect of dehydration/re-hydration on the melting was investigated.  The
     isomalt glass transition, at about 60.degree.C, was studied on samples
     cooled after melting.  The dynamic aspect of structural relaxation of
     isomalt was quantified by its fragility parameter.  Glassy state
     stability was evaluated by performing ageing expts. at sub-Tg
     temps.  During ageing, apart from the expected enthalpy relaxation
     effects, isomalt showed a peculiar behavior, due to its isomeric compn.
     These preliminary and phenomenol. results were interpreted in terms of
     isomer structure and of carbohydrate-water interactions in the mixt.
CC   17-2 (Food and Feed Chemistry)
     Section cross-reference(s): 33
ST   isomalt dehydration melting structural relaxation glass
     transition
IT   Aging, materials
       Drying
     Evaporation enthalpy
     Fusion enthalpy
       Glass transition
     Structural phase transition
     Structural relaxation
        (of isomalt)
```

IT Aging, materials
Drying
Evaporation enthalpy
Fusion enthalpy
Glass transition
Structural phase transition
Structural relaxation
(of isomalt)
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 2 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:792225 HCAPLUS
DOCUMENT NUMBER: 135:335183
TITLE: Stable **glassy** state powder formulations for proteinaceous and other drugs
INVENTOR(S): Foster, Linda C.; Kuo, Mei-chang; Billingsley, Shelia R.
PATENT ASSIGNEE(S): Inhale Therapeutic Systems, USA
SOURCE: U.S., 38 pp., Cont.-in-part of U.S. Ser. No. 733,225.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6309671	B1	20011030	US 1997-950385	19971014
US 6258341	B1	20010710	US 1996-733225	19961017
AU 9923695	A1	19990708	AU 1999-23695	19990409
AU 740760	B2	20011115		

PRIORITY APPLN. INFO.: US 1995-423515 B2 19950414
WO 1996-US5070 A2 19960412
US 1996-733225 A2 19961017
AU 1996-54827 A3 19960412

AB A powd., dispersible compn. suitable for inhalation having stable dispersibility over time is provided. The compn. exhibits a characteristic glass transition temp. (Tg) and a recommended storage temp. (Ts), wherein the difference between Tg and Ts is at least about 10.degree. (i.e., Tg-Ts is greater than 10.degree.). The compn. comprises a mixt. of a pharmaceutically-acceptable glassy matrix and at least one pharmacol. active material within the glassy matrix. It may be further mixed with a powd., pharmaceutically-acceptable carrier. It is particularly valuable in unit dosage form having a moisture barrier, in combination with appropriate labeling instructions. A process for producing a powd. dispersible compn. is also provided, wherein the process comprises removing the solvent from a soln. comprising a solvent, a glass former and a pharmacol. active material under conditions sufficient to form a glassy matrix having the pharmacol. active material within the matrix. For example, a 60% insulin compn. that maintained protein integrity and aerosol **stability** after storage at 30.degree., 40.degree., 50.degree., and temp. cycling at 2-37.degree. was prepd. by spray drying of a soln. contg. 7.5 mg human zinc insulin, 1.27 mg mannitol, 3.38 mg sodium citrate, 0.026 mg sodium hydroxide, and 0.32 mg glycine per mL of water for a total solids concn. of 12.5 mg/mL at pH 7.3. The dry powder obtained contained 60.0% insulin, 2.6% glycine, 27.1% sodium citrate, 10.1% mannitol, and 0.2% sodium ion from sodium hydroxide. This formulation was remarkable in the fact that the powder could take up to 4.6% moisture without a loss of aerosol performance.

IC ICM A61K009-14
NCL 424489000
CC 63-6 (Pharmaceuticals)
ST protein drug **glassy** matrix powder inhalant
IT Humidity
(absorption; stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT Lung
(administration by; stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT Drug delivery systems
(aerosols, powders; stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT Containers
(moisture barrier-contg.; stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT Absorption
(moisture; stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT Drug delivery systems
(powders, inhalants; stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT Particle size
(prepn. of stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT Interleukin 1 receptors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(recombinant; stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT Carboxylic acids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(salts; stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT Albumins, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serum; stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT Evaporation
Precipitation (chemical)
(solvent removal by; prepn. of stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT **Drying**
(**spray**, solvent removal by; prepn. of stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT Storage
(stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT Amino acids, biological studies
Carbohydrates, biological studies
Caseins, biological studies
Peptides, biological studies
Polymers, biological studies
Polysaccharides, biological studies
Proteins, general, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT **Glass** transition temperature
(stable **glassy** state powders with characteristic **glass** transition temp. suitable for inhalation)

IT **69-65-8**, D-**Mannitol** 77-86-1, Tromethamine 77-92-9, Citric acid, biological studies 1185-53-1, Tromethamine hydrochloride 9000-69-5, Pectin 9003-39-8, Povidone
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stable **glassy** state powders suitable for inhalation for proteinaceous and other drugs)

IT 57-50-1, Sucrose, biological studies 63-42-3, Lactose 69-79-4, Maltose 99-20-7, Trehalose 470-55-3, Stachyose 512-69-6, Raffinose 528-50-7, Cellobiose 994-36-5, Sodium citrate 1109-28-0, Maltotriose 3632-91-5, Magnesium gluconate 8049-62-5, Zinc insulin 9004-10-8, Insulin, biological studies 9005-27-0, Hydroxyethyl starch 9041-92-3, .alpha.1-Antitrypsin 9050-36-6, Maltodextrin 12619-70-4, Cyclodextrin 18559-94-9, Albuterol 47931-85-1, Salmon calcitonin 51022-70-9, Albuterol sulfate 60731-46-6, Elcatonin 63213-92-3 68424-04-4, Polydextrose 134613-11-9
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 3 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:416803 HCAPLUS
DOCUMENT NUMBER: 135:24708
TITLE: A rapid acting freeze-**dried** oral pharmaceutical composition for treating migraine
INVENTOR(S): Venkateswara Rao, Pavuluri; Khadgapathi, Podili
PATENT ASSIGNEE(S): Natco Pharma Limited, India
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001039836	A1	20010607	WO 2000-IN78	20000825

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: IN 1999-MA1160 A 19991201

AB The present invention relates to a novel rapid-acting freeze-dried pharmaceutical compn. useful for the treatment of migraine and assocd. symptoms at a reduced total dose of active substance than required for oral administration in the form of a tablet. The compn. contains a porous matrix network of a water sol. or water dispersible carrier material, a pharmaceutically active substance(s), organoleptic additives such as sweetening agents, flavoring agents, and coloring agents, pharmaceutically acceptable preservatives, solubilizing agents, surface active agents and/or buffering agents. The pharmaceutical compn. optionally may contain other additives such as permeation enhancers, chelating salts and **stabilizing** agents. Advantages of the invention are: (1) rapid onset of action due to the rapid absorption of the active substance

through oral mucosa, (2) reduced dosage of the drugs as absorption through oral mucosa bypasses the first-pass metab. and overcomes possible degrdn. in the gastrointestinal tract, (3) easy to administer to pediatric and geriatric patients, and (4) medicament can be taken without water. For example, tablets were prepd. by freeze drying to contain sumatriptan succinate 14.00 mg, ondansetron hydrochloride 5.0 mg, citric acid 1.68 mg, Na2HPO4 2.42 mg, polyvinyl chloride 3.0%, mannitol 25%, Me paraben sodium 0.1%, and Pr paraben sodium 0.01%.

IC ICM A61P025-06
ICS A61K031-48; A61K031-42; A61K031-4196; A61K031-4045; A61K031-138; A61K009-19

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1

ST antimigraine oral pharmaceutical **freeze drying**

IT Preservatives
(antimicrobial; rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)

IT Vinyl compounds, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carboxy-contg., polymers; rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)

IT Gelatins, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydrolyzates; rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)

IT Mouth
(mucosa, absorption by; rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)

IT Drug delivery systems
(oral; rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)

IT Antimicrobial agents
(preservatives; rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)

IT Adrenoceptor agonists
Allergy inhibitors
Analgesics
Anti-inflammatory agents
Antiemetics
Antihistamines
Antimigraine agents
Buffers
Coloring materials
Flavoring materials
Freeze drying
Solubilizers
Stabilizing agents
Surfactants
Sweetening agents
(rapid-acting **freeze-dried** oral pharmaceuticals for migraine treatment)

IT Bile salts
Carbohydrates, biological studies
Gelatins, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)

IT Fatty acids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(salts; rapid-acting freeze-**dried** oral pharmaceuticals for

migraine treatment)
IT Drug delivery systems
(tablets; rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)
IT Fatty acids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(unsatd., salts; rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)
IT 113-15-5, Ergotamine 379-79-3, Ergotamine tartrate 525-66-6, Propranolol 99614-01-4, Ondansetron hydrochloride 103628-46-2, Sumatriptan 103628-48-4, Sumatriptan succinate 139264-17-8, Zolmitriptan
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)
IT 58-38-8, Prochlorperazine 58-73-1, Diphenhydramine 90-82-4, Pseudoephedrine 103-90-2, Paracetamol 113-92-8, Chlorpheniramine maleate 364-62-5, Metoclopramide 523-87-5, Dimenhydrinate 9003-39-8, Polyvinylpyrrolidone 14838-15-4, Phenylpropanolamine 26159-34-2, Naproxen sodium 50679-08-8, Terfenadine 52468-60-7, Flunarizine 57808-66-9, Domperidone 83881-51-0, Cetirizine 99614-02-5, Ondansetron 109889-09-0, Granisetron
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)
IT 50-99-7, Dextrose, biological studies 59-23-4, Galactose, biological studies 60-00-4D, Edetic acid, salts 63-42-3, Lactose **69-65-8**, D-**Mannitol** 77-92-9, Citric acid, biological studies 77-92-9D, Citric acid, salts 151-21-3, Sodium lauryl sulfate, biological studies 302-95-4, Sodium deoxycholate 361-09-1, Sodium cholate 516-50-7, Taurodeoxycholic acid 577-11-7, Docusate sodium 863-57-0, Sodium glycocholate 994-36-5, Sodium citrate 1335-30-4, Aluminum **silicate** 5026-62-0, Methylparaben sodium 7558-79-4 7632-05-5, Sodium phosphate 7647-14-5, Sodium chloride, biological studies 9000-69-5, Pectin 9002-89-5, Polyvinylalcohol 9004-32-4, Carboxymethyl cellulose 9004-53-9, Dextrin 9004-62-0, Hydroxyethyl cellulose 9004-64-2, Hydroxypropyl cellulose 9004-67-5, Methyl cellulose 9005-32-7, Alginic acid 12441-09-7D, Sorbitan, esters 12619-70-4, Cyclodextrin 16409-34-0, Sodium glycodeoxycholate 35285-69-9, Propylparaben sodium 57916-92-4, carbomer 934P 151687-96-6, carbomer 974P
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 4 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:3628 HCAPLUS
DOCUMENT NUMBER: 134:233335
TITLE: **Glass** formation by galactopinitol with other sugars and their ability to protect phospholipid vesicles from **drying** damage
AUTHOR(S): Shen, Li-Kuo; Chien, Ching-Te; Lin, Tsan-Piao
CORPORATE SOURCE: Taipei Med. Coll. Hosp., Taipei, 110, Taiwan
SOURCE: Taiwan Linye Kexue (2000), 15(3), 293-301
CODEN: TLKEFF; ISSN: 1026-4469
PUBLISHER: Taiwan Forestry Research Institute

DOCUMENT TYPE: Journal
LANGUAGE: English

AB A galactopinitol (Galpi), O-.alpha.-D-galactopyranosyl-(1.fwdarw.1)-3-O-methyl-D-chiro-inositol, together with sucrose, raffinose, and stachyose were extd. from seeds of Leucaena leucocephala (Lam.) de Wit and characterized for glass formation and phospholipid vesicle **stabilization** during dehydration. Raffinose, stachyose, and Galpi were found to have good glass forming properties, and their glass transition temps. (Tgs) were 67.4, 66.4, and 33.40.degree., resp. The Tgs were much higher than those of glucose and sucrose. The Tg for a mass ratio mixt. of Galpi and sucrose of 0.3/1 was greater than 0 and was similar to that of the same ratio mixt. of raffinose to sucrose, indicating that Galpi as well as oligosaccharides plays an important role in glass formation. The mixt. of Galpi plus sucrose appeared to protect phospholipid vesicles during dehydration and rehydration to the same degree as did raffinose or the stachyose plus sucrose mixt. The percent protection (leakage of isocitrate) of vesicles provided by sucrose, Galpi, raffinose, and stachyose was in the approx. range of 38 to 48%. The results suggest that Galpi may prevent cellular collapse during the desiccation of Leucaena seeds and function much the same as oligosaccharides.

CC 6-6 (General Biochemistry)
Section cross-reference(s): 11

ST **glass** formation galactopinitol sugar Leucaena seed; phospholipid membrane **drying** protection galactopinitol sugar Leucaena seed

IT Membrane, biological
(bilayer; **glass** formation by galactopinitol from Leucaena leucocephala seeds with other sugars and ability to protect phospholipid vesicles from **drying** damage)

IT **Drying**
Glass transition temperature
Leucaena glauca
Seed
(**glass** formation by galactopinitol from Leucaena leucocephala seeds with other sugars and ability to protect phospholipid vesicles from **drying** damage)

IT Oligosaccharides, biological studies
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(**glass** formation by galactopinitol from Leucaena leucocephala seeds with other sugars and ability to protect phospholipid vesicles from **drying** damage)

IT Phosphatidylserines
RL: NUU (Other use, unclassified); USES (Uses)
(membrane bilayers contg.; **glass** formation by galactopinitol from Leucaena leucocephala seeds with other sugars and ability to protect phospholipid vesicles from **drying** damage)

IT 57-50-1, Sucrose, biological studies 470-55-3, Stachyose 512-69-6, Raffinose 178152-64-2, O-.alpha.-D-Galactopyranosyl-(1.fwdarw.1)-3-O-methyl-D-chiro-**inositol**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(**glass** formation by galactopinitol from Leucaena leucocephala seeds with other sugars and ability to protect phospholipid vesicles from **drying** damage)

IT 57-50-1, Sucrose, biological studies 470-55-3, Stachyose 512-69-6, Raffinose 178152-64-2, O-.alpha.-D-Galactopyranosyl-(1.fwdarw.1)-3-O-methyl-D-chiro-**inositol**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)

(**glass** formation by galactopinitol from Leucaena leucocephala seeds with other sugars and ability to protect phospholipid vesicles from **drying** damage)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 5 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:700669 HCAPLUS
DOCUMENT NUMBER: 133:366299
TITLE: Effects of lyophilization on the physical characteristics and chemical **stability** of **amorphous** quinapril hydrochloride
AUTHOR(S): Guo, Yushen; Byrn, Stephen R.; Zografi, George
CORPORATE SOURCE: School of Pharmacy, University of Wisconsin-Madison, Madison, WI, 53706, USA
SOURCE: Pharmaceutical Research (2000), 17(8), 930-935
CODEN: PHREEB; ISSN: 0724-8741
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Purpose. To prep. amorphous quinapril-HCl (QHCl) by lyophilization and to compare its phys. characteristics and chem. stability as a function of the initial pH of the pre-lyophilized soln. Methods. Amorphous QHCl samples were prepd. by lyophilization from aq. solns. Solid-state characteristics were evaluated by DSC, PXRD, and optical microscopy. Chem. degrdn. was monitored by an HPLC assay. Results. Amorphous QHCl samples obtained from lyophilization showed variable glass transition temps., depending on the pH and/or concn. of the starting aq. solns. Neutralized quinapril (Q) in the amorphous form, which has a Tg of 51.degree., lower than that of its HCl salt (91.degree.), was significantly more reactive than QHCl at the same temp. The Tg of lyophilized samples prepd. at various initial pH values correlated well with values predicted for mixts. of QHCl and Q. Their different reaction rates were related to their glass transition temp., consistent with the results from earlier studies obtained with amorphous samples made by pptn. from an org. soln. and grinding of the crystal solvate. Conclusions. Lyophilization of different QHCl solns. produces mixts. of amorphous QHCl and its neutralized from Q, with Tg values intermediate to the values of QHCl and Q. As the fraction of Q increases the overall rate of chem. degrdn. increases relative to QHCl alone, primarily due to the increase in mol. mobility induced by the plasticizing effects of Q.

CC 63-5 (Pharmaceuticals)
ST lyophilization phys property **amorphous** quinapril; **stability amorphous** quinapril
IT Decomposition
Decomposition kinetics
Freeze drying
Glass transition temperature
Grinding (size reduction)
(lyophilization effect on phys. characteristics and **stability** of **amorphous** quinapril)
IT 103733-49-9
RL: FMU (Formation, unclassified); FORM (Formation, nonpreparative)
(lyophilization effect on phys. characteristics and **stability** of **amorphous** quinapril)
IT 85441-61-8, Quinapril
RL: FMU (Formation, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); USES (Uses)
(lyophilization effect on phys. characteristics and **stability**

of **amorphous** quinapril)
IT 85441-61-8, Quinapril
RL: FMU (Formation, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); USES (Uses)
(lyophilization effect on phys. characteristics and **stability** of **amorphous** quinapril)
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 6 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:567322 HCAPLUS
DOCUMENT NUMBER: 134:76246
TITLE: Evaluation of physicochemical **stability** of **amorphous** cefditoren pivoxil, using modulated-temperature differential scanning calorimetry
AUTHOR(S): Ohta, Masato; Tozuka, Yuichi; Oguchi, Toshio; Yamamoto, Keiji
CORPORATE SOURCE: Pharmaceutical Research Center, Meiji Seika Kaisha, Ltd, Yokohama, 222-8567, Japan
SOURCE: Yakuzaigaku (2000), 60(2), 160-165
CODEN: YAKUA2; ISSN: 0372-7629
PUBLISHER: Nippon Yakuzai Gakkai
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Amorphous of cefditoren pivoxil was prepd. by grinding or spray-drying. When the amorphous samples were stored at 40.degree. and 96% relative humidity (RH) or heated by using DSC, crystn. was not obsd. for the spray-dried sample, but it was obsd. for the ground sample. Glass transition accompanying enthalpy relaxation was evaluated for the spray-dried and the ground cefditoren pivoxil by modulated-temp. differential scanning calorimetry (MTDSC). Glass transition temp. (Tg) and relaxation enthalpy (.DELTA.H) of the ground samples were varied by storage at a temp. below Tg, but for the spray-dried sample no significant change in Tg or .DELTA.H was obsd. by storage. The ground sample was less stable and it was stabilized by storage below Tg, but the spray-dried sample was more stable. Since the energy level of the amorphous region between spray-dried and ground samples was different, the difference of the crystn. of the amorphous samples could be obsd. by storage at 40.degree. and 96% RH or heating by using DSC.
CC 63-5 (Pharmaceuticals)
ST physicochem **stability** **amorphous** cefditoren pivoxil DSC
IT Differential scanning calorimetry
Glass transition temperature
Grinding (size reduction)
Recrystallization
Relaxation enthalpy
Storage
(physicochem. **stability** of **amorphous** cefditoren pivoxil by modulated-temp. DSC)
IT Humidity
(relative; physicochem. **stability** of **amorphous** cefditoren pivoxil by modulated-temp. DSC)
IT **Drying**
(**spray**; physicochem. **stability** of **amorphous** cefditoren pivoxil by modulated-temp. DSC)
IT **Drying**
(**spray**; physicochem. **stability** of **amorphous** cefditoren pivoxil by modulated-temp. DSC)

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 7 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:128413 HCAPLUS
DOCUMENT NUMBER: 132:236144
TITLE: Storage **stability** of freeze-**dried** starter cultures (Streptococcus thermophilus) as related to physical state of freezing matrix
AUTHOR(S): Andersen, Astrid B.; Fog-Petersen, Mette S.; Larsen, Heidi; Skibsted, Leif H.
CORPORATE SOURCE: Food Chemistry, Department of Dairy and Food Science, Royal Veterinary and Agricultural University, Frederiksberg, DK-1958, Den.
SOURCE: Lebensm.-Wiss. Technol. (1999), 32(8), 540-547
CODEN: LBWTAP; ISSN: 0023-6438
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The temp. dependence for loss of acidification activity during storage of a freeze-dried skimmed milk based starter culture of Streptococcus thermophilus in a matrix of ascorbic acid, casein and sucrose or mannitol showed Arrhenius behavior below the glass transition temp. (Tg as detd. by differential scanning calorimetry), with an energy of activation depending on the sugar with 57 kJ/mol for sucrose and 40 kJ/mol for mannitol, but not on the initial concn. of sugar before freezing (60 g/kg or 120 g/kg of dry matter). For storage at or above Tg (Tg was around 50.degree.C), loss of activity increased dramatically with non-Arrhenius temp. dependence. Mannitol based glasses yielded better protection for aerobic storage and this was probably due to better antioxidative properties. (c) 1999 Academic Press.
CC 17-8 (Food and Feed Chemistry)
ST Streptococcus starter **freeze drying** sugar **glass**
IT Cryoprotectants
Freeze drying
Glass transition
Streptococcus thermophilus
(storage **stability** of **freeze-dried** starter cultures (Streptococcus thermophilus) as related to phys. state of **freezing** matrix)
IT Carbohydrates, biological studies
RL: FFD (Food or feed use); PEP (Physical, engineering or chemical process); BIOL (Biological study); PROC (Process); USES (Uses)
(storage **stability** of freeze-**dried** starter cultures (Streptococcus thermophilus) as related to phys. state of freezing matrix)
IT 57-50-1, Sucrose, biological studies **69-65-8, Mannitol 87-89-8, Inositol** 9050-36-6, Maltodextrin
RL: FFD (Food or feed use); PEP (Physical, engineering or chemical process); BIOL (Biological study); PROC (Process); USES (Uses)
(storage **stability** of freeze-**dried** starter cultures (Streptococcus thermophilus) as related to phys. state of freezing matrix)
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 8 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:613714 HCAPLUS
DOCUMENT NUMBER: 131:248244

TITLE: **Amorphous glasses** for **stabilizing** sensitive products
INVENTOR(S): Roser, Bruce Joseph; De Castro, Arcadio Garcia
PATENT ASSIGNEE(S): Cambridge Biostability Limited, UK
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9947174	A1	19990923	WO 1999-GB820	19990317
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9929451	A1	19991011	AU 1999-29451	19990317
EP 1071465	A1	20010131	EP 1999-910516	19990317
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.:

GB 1998-5699	A	19980318
GB 1998-20689	A	19980923
WO 1999-GB820	W	19990317

AB A method of drying, without damage, a compd. which is subject to deactivation on drying, or a mixt. of such compds., comprises subjecting an aq. system contg. the compd. or mixt. to drying in the presence of .gtoreq.1 chem. inert monosaccharide sugar alc. and .gtoreq.1 additive which is a glass-former or a glass formation **facilitator**, whereby the compd. solidifies from soln. as an amorphous glass rather than by forming crystals. This method is useful for drying compds. at or above room temp. which are otherwise subject to deactivation on drying. Thus, alk. phosphatase, vacuum-dried or freeze-dried in a glass-forming blend of mannitol 30, inositol 15, galactitol 15, and Byco C (degraded gelatin) 40%, was stable during storage at 37.degree. or 50.degree. for 5 wk.

IC ICM A61K047-26
ICS A61K047-22; A23L001-275; A61K007-00; A61K009-00
CC 63-6 (Pharmaceuticals)
ST **sugar alc glass stabilizer**
protein; heat **stabilizer** protein hexitol **glass**
IT Phycoerythrins
RL: PEP (Physical, engineering or chemical process); PROC (Process)
(R-phycoerythrins; **amorphous glasses** for **stabilizing** sensitive products)
IT Denaturation
Drying
Freeze drying
Stabilizing agents
(**amorphous glasses** for **stabilizing** sensitive products)
IT **Glass**, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**amorphous glasses** for **stabilizing** sensitive products)

IT Gelatins, biological studies
Peptides, biological studies
Phosphates, biological studies
Silicates, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**glasses** contg.; **amorphous glasses** for **stabilizing** sensitive products)

IT **Alditols**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**glasses**; **amorphous glasses** for **stabilizing** sensitive products)

IT Crystallization
(inhibitors; **amorphous glasses** for **stabilizing** sensitive products)

IT Fluorescent substances
(proteins, **stabilization** of; **amorphous glasses** for **stabilizing** sensitive products)

IT Albumins, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serum, crystn. inhibitors; **amorphous glasses** for **stabilizing** sensitive products)

IT **Drying**
(**spray**; **amorphous glasses** for **stabilizing** sensitive products)

IT Blood serum
Vaccines
(**stabilization** of; **amorphous glasses** for **stabilizing** sensitive products)

IT Antibodies
Antigens
Complement
Enzymes, biological studies
Nucleic acids
Polysaccharides, biological studies
Proteins, general, biological studies
RL: BAC (Biological activity or effector, except adverse); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**stabilization** of; **amorphous glasses** for **stabilizing** sensitive products)

IT **Drying**
(**vacuum**; **amorphous glasses** for **stabilizing** sensitive products)

IT 9001-78-9 11096-26-7, Erythropoietin
RL: BAC (Biological activity or effector, except adverse); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**amorphous glasses** for **stabilizing** sensitive products)

IT 99-20-7, Trehalose 64519-82-0, Palatinit
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(crystn. inhibitor; **amorphous glasses** for **stabilizing** sensitive products)

IT 64-19-7D, Acetic acid, salts **69-65-8**, D-**Mannitol** **87-89-8**, myo-**Inositol** **87-99-0**, **Xylitol** 488-81-3, Adonitol **608-66-2**, **Galactitol** 814-80-2, Calcium lactate 1330-43-4D, Sodium tetraborate, salts 1332-77-0D, Potassium tetraborate, salts **2152-56-9**, **Arabinitol** 9003-39-8D, PVP, salts 9004-54-0, Dextran, biological studies 10043-35-3D, Boric acid, salts 11129-12-7, Borate

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**glasses** contg.; **amorphous glasses** for **stabilizing** sensitive products)
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 9 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:451206 HCAPLUS
DOCUMENT NUMBER: 131:92515
TITLE: Amylin agonist peptides for **stabilization** of insulin injections
INVENTOR(S): L'Italian, James; Musunuri, Shankar; Ruby, Cale
PATENT ASSIGNEE(S): Amylin Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9934822	A1	19990715	WO 1998-US288	19980109
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9859094	A1	19990726	AU 1998-59094	19980109
EP 1044015	A1	20001018	EP 1998-902423	19980109
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: WO 1998-US288 A 19980109

AB The present invention is concerned with a pharmaceutical formulation in a container, for example, a vial, prefilled cartridge, prefilled syringe or disposable pen, comprising approx. 0.01 to about 0.5 % (w/v) amylin agonist, preferably pramlintide, in an aq. system along with approx. 0.02 to about 0.5 % (w/v) of an acetate, phosphate, citrate, or glutamate buffer to a pH of the final compn. of approx. 3.0 to about 6.0 as well as approx. 1.0 to 10 % (w/v) of a carbohydrate or polyhydric alc. tonicifier; and, optionally, approx. 0.005 to 1.0 % (w/v) of a preservative selected from the group consisting of m-cresol, benzyl alc., parabens and phenol. These formulations maintain **stability** upon storage under refrigerated or room temp. conditions. Such formulations can be further combined with insulin in the same syringe for administration to a patient.

IC ICM A61K038-28
ICS A61K030-00; C07K007-10
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 2
IT Buffers
Preservatives
Surfactants
Vials
(amylin-agonist peptides for **stabilization** of insulin injections)
IT Peptides, biological studies
RL: BAC (Biological activity or effector, except adverse); THU

(Therapeutic use); BIOL (Biological study); USES (Uses)
(amylin-agonist peptides for **stabilization** of insulin injections)

IT Polyoxyalkylenes, uses
RL: NUU (Other use, unclassified); PEP (Physical, engineering or chemical process); PROC (Process); USES (Uses)
(amylin-agonist peptides for **stabilization** of insulin injections)

IT Carbohydrates, processes
RL: PEP (Physical, engineering or chemical process); PROC (Process)
(amylin-agonist peptides for **stabilization** of insulin injections)

IT Phosphates, uses
RL: NUU (Other use, unclassified); PEP (Physical, engineering or chemical process); PROC (Process); USES (Uses)
(buffer; amylin-agonist peptides for **stabilization** of insulin injections)

IT Medical goods
(containers; amylin-agonist peptides for **stabilization** of insulin injections)

IT Borosilicate **glasses**
RL: DEV (Device component use); USES (Uses)
(containers; amylin-agonist peptides for **stabilization** of insulin injections)

IT Drug delivery systems
(freeze-**dried**; amylin-agonist peptides for **stabilization** of insulin injections)

IT Drug delivery systems
(injections; amylin-agonist peptides for **stabilization** of insulin injections)

IT Drug delivery systems
(liqs.; amylin-agonist peptides for **stabilization** of insulin injections)

IT Containers
(medical; amylin-agonist peptides for **stabilization** of insulin injections)

IT Surfactants
(nonionic; amylin-agonist peptides for **stabilization** of insulin injections)

IT Physiological saline solutions
(phosphate-buffered; amylin-agonist peptides for **stabilization** of insulin injections)

IT Alcohols, processes
RL: PEP (Physical, engineering or chemical process); PROC (Process)
(polyhydric; amylin-agonist peptides for **stabilization** of insulin injections)

IT 106602-62-4, Amylin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(agonists; amylin-agonist peptides for **stabilization** of insulin injections)

IT 151126-32-8, Pramlintide
RL: BAC (Biological activity or effector, except adverse); PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(amylin-agonist peptides for **stabilization** of insulin injections)

IT 50-69-1, Ribose 50-70-4, Sorbitol, uses 56-81-5, 1,2,3-Propanetriol, uses 63-42-3, Lactose **69-65-8, Mannitol** 69-79-4, Maltose **87-89-8, Inositol 87-99-0, Xylitol** 94-13-3, Propyl paraben 94-26-8, Butyl paraben

99-20-7, Trehalose 99-76-3, Methyl paraben 100-51-6, Benzyl alcohol, uses 108-39-4, uses 108-95-2, Phenol, uses 120-47-8, Ethyl paraben 3458-28-4, Mannose 8012-39-3, Citrate buffer 9002-92-0 9003-11-6 9005-65-6 25322-68-3 75621-03-3 106392-12-5, Poloxamer
RL: NUU (Other use, unclassified); PEP (Physical, engineering or chemical process); PROC (Process); USES (Uses)
(amylin-agonist peptides for **stabilization** of insulin injections)

IT 9004-10-8, Insulin, biological studies 11061-68-0, Humulin
RL: PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(amylin-agonist peptides for **stabilization** of insulin injections)

IT 56-86-0, Glutamic acid, uses 64-19-7, Acetic acid, uses
RL: NUU (Other use, unclassified); PEP (Physical, engineering or chemical process); PROC (Process); USES (Uses)
(buffer; amylin-agonist peptides for **stabilization** of insulin injections)

IT 56-86-0, Glutamic acid, uses 64-19-7, Acetic acid, uses
RL: NUU (Other use, unclassified); PEP (Physical, engineering or chemical process); PROC (Process); USES (Uses)
(buffer; amylin-agonist peptides for **stabilization** of insulin injections)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 10 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:295870 HCAPLUS
DOCUMENT NUMBER: 131:45073
TITLE: Formulation of proteins in vacuum-**dried glasses**. II. Process and storage **stability** in sugar-free amino acid systems
AUTHOR(S): Mattern, Markus; Winter, Gerhard; Kohnert, Ulrich; Lee, Geoffrey
CORPORATE SOURCE: Department of Pharmaceutical Technology, Friedrich-Alexander University, Erlangen, 91058, Germany
SOURCE: Pharm. Dev. Technol. (1999), 4(2), 199-208
CODEN: PDTEFS; ISSN: 1083-7450
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The purpose of this research was to investigate the freeze- and vacuum-drying behavior of L-amino acids of current/potential use as adjuvants for formulating proteins. The anal. methods used were wide-angle x-ray diffraction, differential scanning calorimetry, and SEM. Protein anal. was performed either as an activity assay (lactate dehydrogenase [LDH]) or by size-exclusion chromatog. (granulocyte colony-stimulating factor [rhG-CSF]). After samples were freeze-dried, only the four basic amino acids (arginine, lysine, histidine, and citrulline) formed amorphous solids, which, however, were partially cryst. The remaining amino acids all formed fully cryst. solids. After samples were vacuum-dried (20.degree., 0.1 mbar, 1 mL fill vol. in 2-mL vials), fully cryst. solids were formed by all of the amino acids. For arginine, the addn. of either HCl, H3PO4, or H2SO4 sufficient to form the resp. salt produced amorphous solids after vacuum-drying, but they had high residual water contents and low glass transition temps. (Tg). Addn. of phenylalanine to arginine base inhibited crystn. of the latter at low concns. during vacuum-drying procedure, leading to formation of a pure rubbery solid. At higher concns. the phenylalanine crystd., producing dry

products with glass transition temps. of >60.degree.. The process and storage stability of LDH and rhG-CSF in the vacuum-dried phenylalanine/arginine glasses was greatly improved at temps. up to 40.degree. compared with the unprotected proteins. Uptake of moisture during storage was, however, a complicating factor, reducing Tg, promoting crystn., and leading to decreased protein stability. The PO4 salt of arginine produced esp. high glass transition temps. after it was vacuum-dried. These sugar-free amino acid formulations thus are potential stabilizers for proteins.

CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 63

ST amino acid **drying** storage

IT **Freeze drying**
Storage
(amino acids which form **amorphous glasses** during **freeze-** or **vacuum-drying** procedures)

IT Amino acids, properties
Proteins, general, properties
RL: PRP (Properties)
(amino acids which form **amorphous glasses** during **freeze-** or **vacuum-drying** procedures)

IT 52-90-4, L-Cysteine, properties 56-40-6, Glycine, properties 56-41-7, L-Alanine, properties 56-45-1, L-Serine, properties 56-87-1, L-Lysine, properties 61-90-5, L-Leucine, properties 63-68-3, L-Methionine, properties 63-91-2, L-Phenylalanine, properties 71-00-1, L-Histidine, properties 72-18-4, L-Valine, properties 72-19-5, L-Threonine, properties 73-32-5, L-Isoleucine, properties 74-79-3, L-Arginine, properties 147-85-3, L-Proline, properties 372-75-8, L-Citrulline 2835-81-6, .alpha.-Aminobutyric acid 9001-60-9 121181-53-1, RhG-CSF
RL: PRP (Properties)
(amino acids which form **amorphous glasses** during **freeze-** or **vacuum-drying** procedures)

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 11 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:292570 HCAPLUS
DOCUMENT NUMBER: 130:329204
TITLE: Process for producing **dry**, **amorphous** products comprising biologically active materials by convection **drying**, especially **spray drying**
INVENTOR(S): Gabel, Rolf-Dieter; Mattern, Markus; Winter, Gerhard; Wirl, Alexander; Woog, Heinrich
PATENT ASSIGNEE(S): Roche Diagnostics G.m.b.H., Germany
SOURCE: Eur. Pat. Appl., 21 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 913177	A1	19990506	EP 1997-119112	19971103
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
EP 913178	A1	19990506	EP 1998-120455	19981029
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

BR 9804739	A	19991109	BR 1998-4739	19981030
ZA 9810002	A	19990503	ZA 1998-10002	19981102
NO 9805096	A	19990504	NO 1998-5096	19981102
AU 9890459	A1	19990520	AU 1998-90459	19981102
JP 11228389	A2	19990824	JP 1998-311629	19981102
CN 1222403	A	19990714	CN 1998-123864	19981103

PRIORITY APPLN. INFO.: EP 1997-119112 A 19971103

AB A soln. or suspension of a biol. active material (e.g. protein) and a **stabilizing** mixt. of a carbohydrate and a zwitterion with a polar or nonpolar group (e.g. an amino acid), or .gtoreq.2 zwitterions or derivs. thereof, is subjected to convection drying at a relative humidity of <70% and an inlet air temp. of <300.degree. to produce an amorphous or partially amorphous, homogeneous powd. product comprising uniform (esp. spherical) particles and having a glass transition temp. .gtoreq.20.degree. (preferably .gtoreq.40.degree.) and a residual moisture content <8%. The product is stable for .gtoreq.12 mo and has a d. .gtoreq.15% higher than that of lyophilizates. Thus, a mixt. of sucrose (50 mg/mL), L-arginine (10 mg/mL), and L-phenylalanine (10 mg/mL) was spray dried at an inlet air temp. of 100.degree.. The product had residual water content 3.2%, d. 1.023 g/cm3, and glass transition temp. 57.6.degree..

IC ICM B01D001-14
ICS B01D001-18; A61K009-14; F26B003-02

CC 63-6 (Pharmaceuticals)

ST protein **spray drying** carbohydrate amino acid

IT Animal virus
(components; process for producing **dry, amorphous** products comprising biol. active materials by **spray drying**)

IT **Drying**
(convective; process for producing **dry, amorphous** products comprising biol. active materials by **spray drying**)

IT Animal cells
Diagnostic agents
Fluidized bed **drying**
Glass transition temperature
Powders (drug delivery systems)
Spray drying
Stabilizing agents
Vaccines
Zwitterions
(process for producing **dry, amorphous** products comprising biol. active materials by **spray drying**)

IT Antibodies
Coenzymes
DNA
Enzymes, biological studies
Glycoproteins (general), biological studies
Immunoglobulin fragments
Lipoproteins
Peptides, biological studies
Proteins (general), biological studies
RNA
RL: BAC (Biological activity or effector, except adverse); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(process for producing **dry, amorphous** products comprising biol. active materials by **spray drying**)

IT Amino acids, biological studies

Carbohydrates, biological studies
Monosaccharides
Oligosaccharides, biological studies
Polysaccharides, biological studies
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(process for producing **dry**, **amorphous** products comprising biol. active materials by **spray drying**)

IT Drug delivery systems
(**spray-dried**; process for producing **dry**, **amorphous** products comprising biol. active materials by **spray drying**)

IT 11096-26-7D, Erythropoietin, dimers
RL: BAC (Biological activity or effector, except adverse); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(process for producing **dry**, **amorphous** products comprising biol. active materials by **spray drying**)

IT 52-90-4, L-Cysteine, biological studies 56-40-6, Glycine, biological studies 56-41-7, L-Alanine, biological studies 56-84-8, L-Aspartic acid, biological studies 56-86-0, L-Glutamic acid, biological studies 56-87-1, L-Lysine, biological studies 57-48-7, D-Fructose, biological studies 57-50-1, Sucrose, biological studies 61-90-5, L-Leucine, biological studies 63-42-3, Lactose 63-68-3, L-Methionine, biological studies 63-91-2, L-Phenylalanine, biological studies **69-65-8**, D-**Mannitol** 71-00-1, L-Histidine, biological studies 72-18-4, L-Valine, biological studies 73-22-3, L-Tryptophan, biological studies 73-32-5, L-Isoleucine, biological studies 74-79-3, L-Arginine, biological studies 372-75-8, L-Citrulline 2361-96-8, Acetyl-L-phenylalanine ethyl ester 9004-65-3, Hydroxypropylmethylcellulose
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(process for producing **dry**, **amorphous** products comprising biol. active materials by **spray drying**)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 12 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:31050 HCAPLUS
DOCUMENT NUMBER: 130:227652
TITLE: Effects of Additives on the **Stability** of Humicola lanuginosa Lipase during **Freeze-Drying** and Storage in the **Dried** Solid
AUTHOR(S): Kreilgaard, Lotte; Frokjaer, Sven; Flink, James M.; Randolph, Theodore W.; Carpenter, John F.
CORPORATE SOURCE: Department of Pharmaceutical Sciences School of Pharmacy, University of Colorado Health Sciences Center, Denver, CO, 80262, USA
SOURCE: J. Pharm. Sci. (1999), 88(3), 281-290
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of various classes of additives on the **stability** of a protein with a relatively hydrophobic surface, Humicola lanuginosa lipase (HLL), during lyophilization and storage in the dried solid, were investigated. Prior to lyophilization, it was found that 1M trehalose or 1% Tween 20 caused the protein to ppt. IR spectroscopy indicated that

trehalose "salted-out" native HLL, whereas Tween 20 induced non-native aggregates. Optimal recovery of native protein in the initial dried solid was obtained in the presence of additives which formed an amorphous phase and which had the capacity to hydrogen bond to the dried protein (e.g., trehalose and sucrose). Additives which crystd. during lyophilization (e.g., mannitol) or which remained amorphous, but were unable to hydrogen bond to the dried protein (e.g., dextran), afforded less **stabilization** relative to that seen in the absence of additives. Optimal storage **stability** in the dried solid required that both protein unfolding during lyophilization was minimized and that the formulation was stored at a temp. below its Tg value. Crystn. of sucrose during storage greatly reduced the storage **stability** of HLL. This was attributed to the increased moisture content and the reduced Tg value in the remaining amorphous phase contg. the protein. Sucrose crystn. and the resulting damage to the protein were inhibited by decreasing the mass ratio of sucrose:protein.

CC 63-5 (Pharmaceuticals)

ST additive **stability** lipase **freeze drying** storage

IT Crystallization
Freeze drying
Glass transition temperature
(additives effect on **stability** of lipase during **freeze-drying** and storage in **dried** solid)

IT Proteins (general), biological studies
RL: PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(additives effect on **stability** of lipase during **freeze-drying** and storage in **dried** solid)

IT 9001-62-1, Lipase
RL: PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(Humicola lanuginosa; additives effect on **stability** of lipase during **freeze-drying** and storage in **dried** solid)

IT 57-50-1, Sucrose, biological studies **69-65-8**, D-**Mannitol** 99-20-7, Trehalose 9004-54-0, Dextran, biological studies 9005-64-5, Tween 20
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(additives effect on **stability** of lipase during **freeze-drying** and storage in **dried** solid)

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 13 OF 22 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:797798 HCAPLUS

DOCUMENT NUMBER: 130:129859

TITLE: Effects of additives on the **stability** of recombinant human factor XIII during **freeze-drying** and storage in the **dried** solid

AUTHOR(S): Kreilgaard, Lotte; Frokjaer, Sven; Flink, James M.; Randolph, Theodore W.; Carpenter, John F.

CORPORATE SOURCE: Department of Pharmaceutics, The Royal Danish School of Pharmacy, Copenhagen, 80262, Den.

SOURCE: Arch. Biochem. Biophys. (1998), 360(1), 121-134
CODEN: ABBIA4; ISSN: 0003-9861

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Freeze-drying is often used to improve storage **stability** of therapeutic proteins. In order to obtain a product with optimal storage **stability** it is important to understand the mechanisms by which solutes protect the protein against freeze-drying-induced stresses and also against damage induced during subsequent storage. The objective of the current study was to examine the importance of various mechanisms proposed to account for acute and long-term storage **stability** using recombinant human Factor XIII (rFXIII) as a model protein. Initially, for acute **stability** during freeze-drying, it was found that solutes which formed an amorphous phase **stabilized** rFXIII to a greater degree than solutes which crystd. during freeze-drying. However, only amorphous solutes which were able to hydrogen bond to the protein, and thus preserve the native protein structure in the dried solid, provided optimal acute **stability**. Thus, in addn. to forming an amorphous phase, it was also important to possess the ability to hydrogen bond to the protein. Long-term storage **stability** was optimal in the presence of solutes which formed and maintained amorphous phases with Tg values above the storage temp. and which also preserved the native protein structure during freeze-drying. Solute crystn. during storage compromised storage **stability**. (c) 1998 Academic Press.

CC 63-5 (Pharmaceuticals)

ST additive **stability** factor XIII **freeze drying**

IT Aggregation
Conformation
Freeze drying
Glass transition temperature
(additives effect on **stability** of recombinant human factor XIII during **freeze-drying** and storage in **dried** solid)

IT Polyoxyalkylenes, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(additives effect on **stability** of recombinant human factor XIII during **freeze-drying** and storage in **dried** solid)

IT 57-50-1, Sucrose, biological studies **69-65-8**, D-**Mannitol** 99-20-7, Trehalose 9004-54-0, Dextran, biological studies 9005-64-5, Tween 20 25322-68-3, Polyethylene glycol
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(additives effect on **stability** of recombinant human factor XIII during **freeze-drying** and storage in **dried** solid)

IT 57-50-1, Sucrose, biological studies **69-65-8**, D-**Mannitol** 99-20-7, Trehalose 9004-54-0, Dextran, biological studies 9005-64-5, Tween 20 25322-68-3, Polyethylene glycol
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(additives effect on **stability** of recombinant human factor XIII during **freeze-drying** and storage in **dried** solid)

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 14 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:676230 HCAPLUS
DOCUMENT NUMBER: 130:11754
TITLE: Protein **stability** in the **amorphous**

carbohydrate matrix: relevance to anhydrobiosis
AUTHOR(S): Sun, Wendell Q.; Davidson, Paul; Chan, Hardy S. O.
CORPORATE SOURCE: Department of Biological Sciences, National University of Singapore, Singapore, 119260, Singapore
SOURCE: Biochim. Biophys. Acta (1998), 1425(1), 245-254
CODEN: BBACAQ; ISSN: 0006-3002
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The formation of intracellular glass is proposed to be relevant to protein stabilization and survival of anhydrobiotic organisms in the dry state. The stability of proteins in the amorphous carbohydrate matrix and its relevance to seed survival have been investigated in the present study. Glucose-6-phosphate dehydrogenase (G6PDH) was preserved in the amorphous glucose/sucrose (1:10, wt./wt.) matrix by freeze-drying. The stability of freeze-dried G6PDH was examd. at temps. above and below the glass transition temp. (Tg). The rate of G6PDH inactivation in the amorphous carbohydrate matrix deviated significantly from the Arrhenius kinetics, and conformed to the Williams-Landel-Ferry (WLF) relationship. The temp. dependence of G6PDH inactivation in two sets of samples with different Tg values was compared. Identical temp. dependence of G6PDH inactivation was obsd. after temp. normalization by (T-Tg). Seed survival of Vigna radiata Wilczek (mung bean) showed a similar WLF kinetics at storage temps. T .gtoreq. Tg. In situ protein stability in mung bean embryonic axes was studied using differential scanning calorimetry (DSC). Thermal stability of seed proteins exhibited a strong dependence on the Tg of intracellular glass. These results indicate an important role of the glassy state in protein stabilization. Our data suggest an assocn. between protein stability in intracellular glass and seed survival during storage.
CC 6-3 (General Biochemistry)
Section cross-reference(s): 7, 11
ST protein **stability** carbohydrate **glass** matrix anhydrobiosis; glucose phosphate dehydrogenase **stability** carbohydrate matrix; mung bean seed survival protein **stability**
IT Protein denaturation
(in situ; protein **stability** in **amorphous** carbohydrate **glass** matrix and its relevance to seed survival in anhydrobiotic conditions)
IT **Glass** structure
(intracellular; protein **stability** in **amorphous** carbohydrate **glass** matrix and its relevance to seed survival in anhydrobiotic conditions)
IT Thermal **stability**
(of seed proteins; protein **stability** in **amorphous** carbohydrate **glass** matrix and its relevance to seed survival in anhydrobiotic conditions)
IT Dehydration
Dehydration (physiological)
Drought stress (plant)
Enzyme inhibition kinetics
Freeze drying
Glass transition temperature
Seed
Vigna radiata
(protein **stability** in **amorphous** carbohydrate **glass** matrix and its relevance to seed survival in anhydrobiotic conditions)
IT Carbohydrates, biological studies
Proteins (general), biological studies
RL: BPR (Biological process); PEP (Physical, engineering or chemical

process); PRP (Properties); BIOL (Biological study); PROC (Process)
(protein **stability** in **amorphous** carbohydrate **glass** matrix and its relevance to seed survival in anhydrobiotic conditions)

IT 9001-40-5, Glucose-6-phosphate dehydrogenase
RL: BAC (Biological activity or effector, except adverse); PEP (Physical, engineering or chemical process); PRP (Properties); BIOL (Biological study); PROC (Process)
(protein **stability** in **amorphous** carbohydrate **glass** matrix and its relevance to seed survival in anhydrobiotic conditions)

IT 50-99-7, Glucose, biological studies 57-50-1, Sucrose, biological studies
RL: BPR (Biological process); PEP (Physical, engineering or chemical process); PRP (Properties); BIOL (Biological study); PROC (Process)
(protein **stability** in **amorphous** carbohydrate **glass** matrix and its relevance to seed survival in anhydrobiotic conditions)

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 15 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:624750 HCAPLUS
DOCUMENT NUMBER: 129:335626
TITLE: Physicochemical **stability** of crystalline sugars and their spray-**dried** forms: dependence upon relative humidity and suitability for use in powder inhalers
AUTHOR(S): Naini, Venkatesh; Byron, Peter R.; Phillips, Elaine M.
CORPORATE SOURCE: Barr Lab., Inc., Pomona, NY, 10970, USA
SOURCE: Drug Dev. Ind. Pharm. (1998), 24(10), 895-909
CODEN: DDIPD8; ISSN: 0363-9045
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Lactose, trehalose, sucrose, and mannitol were purchased in cryst. form and fractionated by sieving. Coarse (125-212 .mu.m) and fine (44-74 .mu.m) free-flowing fractions were selected as typical of drug carriers in dry-powder inhalers. In addn. one batch of each sugar was spray-dried to form a respirable powder (>50%, <5 .mu.m). Both fractions and the spray-dried powders were characterized before and after storage for 30 days at <23, 23, 52, 75 and 93% relative humidity (RH) at 25.degree.. Moisture uptake was detd. by thermogravimetric anal. (TGA) validated by Karl Fischer titrn. Sieve fractions (before storage at different RHs) and spray-dried materials (before and after storage) were further characterized by DSC and x-ray powder diffraction (XRPD). All cryst. sieve fractions (except sucrose at 93% RH) were stable at 25.degree. and showed insignificant moisture uptake when exposed to each relative humidity for 30 days. Sucrose dissolved in sorbed moisture at 93% RH. Spray-dried lactose, sucrose, and trehalose, which were collected in the amorphous form, showed moisture uptake, without recrystn., when held for 30 days at 23% RH. These sugars recrystd. as sintered masses and became undispersible at .gtoreq.52% RH. Spray-dried mannitol was apparent 100% cryst. when collected directly from the spray-dryer; it did not show humidity-induced changes.

CC 63-5 (Pharmaceuticals)
ST humidity physicochem **stability** sugar cryst; spray died sugar humidity physicochem **stability**
IT Crystal morphology
Dehydration

Dry powder inhalants (drug delivery systems)
Glass transition temperature
Relative humidity
Sorption
Spray drying
(humidity effect on physicochem. **stability** of cryst. sugars and **spray-dried** forms)

IT Carbohydrates, biological studies
RL: PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(humidity effect on physicochem. **stability** of cryst. sugars and spray-**dried** forms)

IT 57-50-1, Sucrose, biological studies 63-42-3, Lactose **69-65-8, Mannitol** 99-20-7, Trehalose
RL: PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(humidity effect on physicochem. **stability** of cryst. sugars and spray-**dried** forms)

L30 ANSWER 16 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:481842 HCAPLUS
DOCUMENT NUMBER: 129:221117
TITLE: Interaction of lyophilized liposomes with sugar **glasses**
AUTHOR(S): Hingle, M. I.; Lloyd, A. W.; Olliff, C. J.; Maas, J.; Taylor, P.
CORPORATE SOURCE: Pharmacy Dept, University of Brighton, Brighton, BN2 4GJ, UK
SOURCE: Proc. Int. Symp. Controlled Release Bioact. Mater. (1998), 25th, 378-379
CODEN: PCRMEY; ISSN: 1022-0178
PUBLISHER: Controlled Release Society, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Lactose, raffinose, and trehalose interacted with the phosphate moiety of the liposomes in similar ways. A certain molar ratio of sugar to the lipid needs to be present to achieve the liposome **stabilization**.

CC 63-5 (Pharmaceuticals)
ST lyophilized liposome interaction sugar **glass**
IT Cryoprotectants
Freeze drying
Liposomes (drug delivery systems)
Phase transition temperature
Stabilizing agents
(interaction of lyophilized liposomes with sugar **glasses**)

IT Carbohydrates, biological studies
Phospholipids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(interaction of lyophilized liposomes with sugar **glasses**)

IT 63-42-3, Lactose **69-65-8**, D-**Mannitol** 99-20-7, Trehalose 512-69-6, Raffinose 26853-31-6, 1-Palmitoyl-2-oleoylphosphatidylcholine 156817-31-1, 1,2-Dioleoylphosphatidylserine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(interaction of lyophilized liposomes with sugar **glasses**)

L30 ANSWER 17 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:720250 HCAPLUS
DOCUMENT NUMBER: 127:304595
TITLE: **Glassy** state and thermal inactivation of invertase and lactase in **dried**

amorphous matrixes
AUTHOR(S): Schebor, Carolina; Burin, Leila; Buera, Maria P.; Aguilera, Jose M.; Chirife, Jorge
CORPORATE SOURCE: Departamento de Industrias Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Buenos Aires, 1428, Argent.
SOURCE: Biotechnol. Prog. (1997), 13(6), 857-863
CODEN: BIPRET; ISSN: 8756-7938
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The thermal stability of enzymes lactase and invertase in dried, amorphous matrixes of sugars (trehalose, maltose, lactose, sucrose, raffinose) and some other selected systems (casein, PVP, milk) was studied. The glass transition temp. (Tg) was limited as a threshold parameter for predicting enzyme inactivation because (a) enzyme inactivation was obsd. in glassy matrixes, (b) a specific effect of enzyme stabilization by certain matrixes particularly trehalose was obsd., and (c) enzyme stability appeared to depend on heating temp. (T) "per se" rather than (T - Tg). For these reasons, a protective mechanism by sugars related to the maintenance of the tertiary structure of the enzyme was favored. A rapid loss of enzyme (lactase) activity was obsd. in heated sucrose systems at T > Tg, and this was attributed to sucrose crystn. since it is known that upon crystn. the protective effect of sugars is lost. Thus, the stabilizing effect could be indirectly affected by the Tg of the matrix, since crystn. of sugars only occurs above Tg. Trehalose model systems (with added invertase) showed an exceptional stability toward "darkening" (e.g., non-enzymic browning) when heated in the dried state to elevated temps. and for long periods of time.

CC 7-2 (Enzymes)
ST enzyme **stability** milk sugar lactase invertase
IT Milk
Skim milk
(effect on enzyme **stability**; **glassy** state and thermal inactivation of invertase and lactase in **dried** **amorphous** matrixes)
IT Carbohydrates, biological studies
Caseins, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(effect on enzyme **stability**; **glassy** state and thermal inactivation of invertase and lactase in **dried** **amorphous** matrixes)
IT 57-50-1, Sucrose, biological studies 63-42-3, Lactose 69-79-4, Maltose 99-20-7, Trehalose 512-69-6, Raffinose 9003-39-8, Pvp 9050-36-6, Maltodextrin
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(effect on enzyme **stability**; **glassy** state and thermal inactivation of invertase and lactase in **dried** **amorphous** matrixes)
IT 9001-57-4, Invertase 9031-11-2, Lactase
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(**glassy** state and thermal inactivation of invertase and lactase in **dried** **amorphous** matrixes)

L30 ANSWER 18 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:664806 HCAPLUS
DOCUMENT NUMBER: 126:11459

TITLE: Optimizing the Lyophilization Cycle and the Consequences of Collapse on the Pharmaceutical Acceptability of Erwinia L-Asparaginase
AUTHOR(S): Adams, Gerald D. J.; Ramsay, J. Richard
CORPORATE SOURCE: Centre for Applied Microbiology and Research, Porton Down/Salisbury/Wiltshire, SP4 0JG, UK
SOURCE: J. Pharm. Sci. (1996), 85(12), 1301-1305
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The antileukemia enzyme, Erwinia L-asparaginase, occurs as a tetramer which can be dissocd. by the stresses of lyophilization into four subunits (subunit Mr 34 000 Da). Dissocn. can be reduced by adding protectants to the formulation to **stabilize** the biopolymer, while the product should dry to form a pharmaceutically elegant, shelf-stable cake which is readily sol. Using anal. ultracentrifugation, HPLC, and CD we have related structural dissocn. of the enzyme during lyophilization to biol. activity. Additives such as mannitol prevent ablation loss of vial contents and dry to form cosmetically elegant cakes but provide little biol. protection, since during freezing they crystallize and are removed from the prepn. Excipients persisting throughout the cycle in the amorphous state provide improved biol. protection, although high mol. wt. compds. such as Dextran (Mr 70 000 Da) are most effective only during product freezing or storage. Low mol. wt. sugars are protective throughout the cycle although formulations contg. monosaccharides often exhibit low collapse temps. (Tc) measured using a freeze-drying microscope or glass transition temps. (Tg') measured by thermal anal., but these formulations distort as drying progresses to form a collapsed, cosmetically unacceptable cake, with reduced activity, poor **stability**, a high moisture content, and reduced soly. Collapse can be avoided by formulating with disaccharides, which display higher Tc temps. than monosaccharides, or drying below Tc. Dried samples which persist in the amorphous state can also collapse when stored above their solid-state collapse temps. when they decay at a faster rate than predicted by Arrhenius kinetics. The solid-state collapse temp. can be significantly decreased by the diffusion of moisture from the stopper into the dry product resulting in an increase in sample water content. Lyophilization cycle times can be reduced by analyzing collapse characteristics so that the relationship between product temp. and chamber pressure can be controlled so that drying rates can be optimized while ensuring that the product does not melt or collapse during sublimation.

CC 63-5 (Pharmaceuticals)
IT Erwinia
Freeze drying
Glass transition temperature
(optimizing the lyophilization cycle and the consequences of collapse on the pharmaceutical acceptability of Erwinia asparaginase)
IT 50-70-4, D-Glucitol, biological studies 50-99-7, D-Glucose, biological studies 57-50-1, Sucrose, biological studies 63-42-3 **69-65-8**, **Mannitol** 99-20-7, Trehalose 9003-39-8, Pvp 9004-54-0, Dextran, biological studies
RL: MOA (Modifier or additive use); PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(optimizing the lyophilization cycle and the consequences of collapse on the pharmaceutical acceptability of Erwinia asparaginase)
IT 50-70-4, D-Glucitol, biological studies 50-99-7, D-Glucose, biological studies 57-50-1, Sucrose, biological studies 63-42-3 **69-65-8**, **Mannitol** 99-20-7, Trehalose 9003-39-8, Pvp 9004-54-0,

Dextran, biological studies
RL: MOA (Modifier or additive use); PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(optimizing the lyophilization cycle and the consequences of collapse on the pharmaceutical acceptability of Erwinia asparaginase)

L30 ANSWER 19 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:95596 HCAPLUS
DOCUMENT NUMBER: 124:127008
TITLE: Importance of **Glass** Transition Temperature in Accelerated **Stability** Testing of **Amorphous** Solids: Case Study Using a Lyophilized Aspirin Formulation
AUTHOR(S): Duddu, Sarma P.; Weller, Kevin
CORPORATE SOURCE: Department of Pharmaceutical Technologies, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406, USA
SOURCE: J. Pharm. Sci. (1996), 85(3), 345-7
CODEN: JPMSAE; ISSN: 0022-3549
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Detn. of the Tg of a lyophilized system is a crucial step in the design of an accelerated stability study. It was detd. if the hydrolysis rate of an amorphous drug, aspirin, can be explained using classical Arrhenius kinetics near its Tg using a lyophilized hydroxypropyl-.beta.-cyclodextrin-aspirin complex.
CC 63-5 (Pharmaceuticals)
ST **glass** transition temp **stability** drug **amorphous** ; aspirin **amorphous stability glass** transition temp
IT **Glass** temperature and transition
Kinetics of hydrolysis
(importance of **glass** transition temp. in accelerated **stability** testing of **amorphous** solids: study using a lyophilized aspirin formulation)
IT Pharmaceutical dosage forms
(freeze-**dried**, importance of **glass** transition temp. in accelerated **stability** testing of **amorphous** solids: study using a lyophilized aspirin formulation)
IT 50-78-2, Aspirin 57-55-6D, 1,2-Propanediol, ether with .beta.-cyclodextrin, complex with aspirin 7585-39-9D, .beta.-Cyclodextrin, hydroxypropyl ether, complex with aspirin
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(importance of **glass** transition temp. in accelerated **stability** testing of **amorphous** solids: study using a lyophilized aspirin formulation)

L30 ANSWER 20 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:851986 HCAPLUS
DOCUMENT NUMBER: 123:250678
TITLE: Dry stable protein preparations for use as calibrators and control products
INVENTOR(S): Magneson, Gerald R.; Reichenbach, David L.
PATENT ASSIGNEE(S): Genzyme Corp., USA
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9522605	A1	19950824	WO 1995-US2278	19950221
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5547873	A	19960820	US 1994-198430	19940222
CA 2183654	AA	19950824	CA 1995-2183654	19950221
AU 9519295	A1	19950904	AU 1995-19295	19950221
AU 699639	B2	19981210		
EP 748378	A1	19961218	EP 1995-911896	19950221
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 09510345	T2	19971021	JP 1995-522000	19950221

PRIORITY APPLN. INFO.: US 1994-198430 A 19940222
WO 1995-US2278 W 19950221

AB Methods and reagents for **stabilizing** proteins for long-term dry storage and superior recovery of their native protein structure for extended reconstituted **stability** at 2-8.degree.C are described. The reagent prepn. is intended primarily for **stabilization** of plasma proteins uses a defibrinated sodium-free blood plasma that is dried in the presence of a glass-forming sugar, a serum albumin and/or a gelatin, and a potassium salt. Optimization expts. are reported.

IC ICM C12N009-96
ICS G01N031-00; G01N033-48; G01N033-50; G01N033-92; G01N033-543

CC 9-11 (Biochemical Methods)

ST blood serum **drying stabilization** storage; albumin gelatin protein **stabilization drying**; potassium salts protein **drying stabilization**; sugars **glass** forming protein **drying stabilization**

IT Proteins, specific or class
RL: PNU (Preparation, unclassified); PREP (Preparation)
(cytoskeletal, dry **stabilization** and storage of; dry stable protein prepns. for use as calibrators and control products)

IT Blood plasma
(defibrinated, sodium-free, **drying** and **stabilization** of; dry stable protein prepns. for use as calibrators and control products)

IT Enzymes
Myoglobins
RL: PNU (Preparation, unclassified); PREP (Preparation)
(dry **stabilization** and storage of; dry stable protein prepns. for use as calibrators and control products)

IT Carbohydrates and Sugars, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(**glass**-forming; dry stable protein prepns. for use as calibrators and control products)

IT Antibodies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(lipoprotein, in purifn. and **stabilization** of HDL and VLDL; dry stable protein prepns. for use as calibrators and control products)

IT Cytoskeleton
(proteins of, dry **stabilization** and storage of; dry stable protein prepns. for use as calibrators and control products)

IT Lipoproteins
RL: PNU (Preparation, unclassified); PUR (Purification or recovery); PREP (Preparation)

(purifn., dry **stabilization** and storage of; dry stable protein prepns. for use as calibrators and control products)

IT Fibrins
RL: REM (Removal or disposal); PROC (Process)
(serum free of, **drying** and **stabilization** of; dry stable protein prepns. for use as calibrators and control products)

IT Carbohydrates and Sugars, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(**alditols**, **glass**-forming; dry stable protein prepns. for use as calibrators and control products)

IT Lipoproteins
RL: PNU (Preparation, unclassified); PUR (Purification or recovery); PREP (Preparation)
(high-d., purifn., dry **stabilization** and storage of; dry stable protein prepns. for use as calibrators and control products)

IT Lipoproteins
RL: PNU (Preparation, unclassified); PUR (Purification or recovery); PREP (Preparation)
(low-d., purifn., dry **stabilization** and storage of; dry stable protein prepns. for use as calibrators and control products)

IT Lipoproteins
RL: PNU (Preparation, unclassified); PUR (Purification or recovery); PREP (Preparation)
(very-low-d., purifn., dry **stabilization** and storage of; dry stable protein prepns. for use as calibrators and control products)

IT 57-50-1, Sucrose, biological studies 99-20-7, Trehalose
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(as **stabilizer** in dry preservation of proteins; dry stable protein prepns. for use as calibrators and control products)

L30 ANSWER 21 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:66685 HCAPLUS
DOCUMENT NUMBER: 118:66685
TITLE: **Glass** formation of 4''-O-(4-methoxyphenyl)acetyltylosin and physicochemical **stability** of the **amorphous** solid
AUTHOR(S): Yamaguchi, Toshio; Nishimura, Masami; Okamoto, Rokuro; Takeuchi, Tomio; Yamamoto, Keiji
CORPORATE SOURCE: Cent. Res. Lab., Mercian Corp., Fujisawa, 251, Japan
SOURCE: Int. J. Pharm. (1992), 85(1-3), 87-96
CODEN: IJPHDE; ISSN: 0378-5173
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Glass formation of 4''-O-(4-methoxyphenyl)acetyltylosin (I) and the physicochem. stability of amorphous I were investigated. The amorphous form of I was prepd. by spray drying of an I CH2Cl2 soln. The glassy state was confirmed by DSC and the glass transition temp. was 102-103.degree.. Different kinds of the glassy state of I could be obtained by changing the inlet temp. of spray drying. Storage expts. on amorphous powders at 40.degree. and 75% RH revealed that the amorphous powders prepd. at a temp. between the glass transition (Tg) and recrystn. (Tc) temps. were the most stable. A correlation between the stability and the apparent d. was obsd.

CC 63-5 (Pharmaceuticals)
ST tylosin deriv **glass** formation **stability**
IT Crystal morphology
Glass structure
Glass temperature and transition

(of methoxyphenylacetyltylosin, dissoln. and **stability** in relation to)
IT Solution rate
(of methoxyphenylacetyltylosin, **glassy** state effect on)
IT **Drying**
(**spray**, of methoxyphenylacetyltylosin, **glassy** state in relation to)
IT **Drying**
(**spray**, of methoxyphenylacetyltylosin, **glassy** state in relation to)

L30 ANSWER 22 OF 22 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1992:578230 HCAPLUS
DOCUMENT NUMBER: 117:178230
TITLE: Amorphism and physicochemical **stability** of spray-**dried** frusemide
AUTHOR(S): Matsuda, Yoshihisa; Otsuka, Makoto; Onoe, Mika; Tatsumi, Etsuko
CORPORATE SOURCE: Dep. Pharm. Technol., Kobe Women's Coll. Pharm., Kobe, 658, Japan
SOURCE: J. Pharm. Pharmacol. (1992), 44(8), 627-33
CODEN: JPPMAB; ISSN: 0022-3573
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The physicochem. properties of amorphous forms of frusemide, prepd. by spray-drying at 50 or 150.degree., and their hygroscopic stability at 25 and 40.degree., and at 0 and 75% relative humidity was investigated. The glass transition temp. of the amorphous form A was 44.2.degree. as measured by DSC, while that of the amorphous form B was 54.4.degree.. The activation energies for glass transition and crystn. processes were calcd. from the DSC thermograms of amorphous forms A and B, resp. Stability detd. by x-ray diffraction at 0% relative humidity, 25 and 40.degree., suggested that form B was more stable than form A. However, the stability of form A at 75% relative humidity and 25 and 40.degree. was similar to that of form B.
CC 63-5 (Pharmaceuticals)
ST physicochem **stability spray drying** frusemide; **amorphous stability spray drying** frusemide
IT Humidity
(**amorphous** nature and physicochem. **stability** of spray-**dried** frusemide in relation to)
IT Crystal morphology
Crystallization
Glass temperature and transition
Heat of crystallization
Heat of transition
(of spray-**dried** frusemide polymorphs)
IT **Drying**
(**spray**, of frusemide, **amorphous** nature and physicochem. **stability** in relation to)
IT **Drying**
(**spray**, of frusemide, **amorphous** nature and physicochem. **stability** in relation to)

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=> fil wpids
FILE 'WPIDS' ENTERED AT 12:22:21 ON 11 MAR 2002
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FILE LAST UPDATED: 06 MAR 2002              <20020306/UP>
MOST RECENT DERWENT UPDATE            200215   <200215/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

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=> d his

     (FILE 'WPIDS' ENTERED AT 12:07:13 ON 11 MAR 2002)
                DEL  HIS
L1         359181 S GLASS## OR SILICATE#
L2           3699 S ALC? (3A) SUGAR#
L3         267979 S DRYING OR DRIED
L4         387838 S L3 OR DRY
L5             14 S L1 AND L2 AND L3
L6         436361 S STABILI?
L7              5 S L5 AND L6
L8           4150 S SUGAR (6A) ALC?
L9             17 S L1 AND L3 AND L8
L10             5 S L9 AND L6
L11          3757 S MANNITOL#
L12            55 S L1 AND L11 AND L4
L13            18 S L12 AND L6
L14         34764 S GLASS (4A) (FORM? OR FACILITA? )
L15             4 S L14 AND L12
L16             1 S L12 AND DEACTIVA?
L17            24 S L13 OR L10 OR L7 OR L15 OR L16

     FILE 'WPIDS' ENTERED AT 12:22:21 ON 11 MAR 2002

=> d .wp 1-24

L17  ANSWER 1 OF 24  WPIDS COPYRIGHT 2002   DERWENT INFORMATION LTD
AN   2002-105105 [14]   WPIDS
CR   1995-328083 [42]; 1996-476858 [47]; 1996-476861 [47]; 1998-032193 [03];
     1998-251045 [22]; 2000-146860 [13]; 2001-090472 [06]
DNC  C2002-032218
TI   New powdered composition useful for pulmonary disease comprises a
     glassy matrix and an active material.
DC   A11 A96 B07
IN   BILLINGSLEY, S R; FOSTER, L C; KUO, M
PA   (INHA-N) INHALE THERAPEUTIC SYSTEMS
CYC  1
PI   US 6309671    B1 20011030 (200214)*      38p
ADT  US 6309671 B1 CIP of US 1995-423515 19950414, CIP of WO 1996-US5070
     19960412, CIP of US 1996-733225 19961017, US 1997-950385 19971014
```

PRAI US 1997-950385 19971014; US 1995-423515 19950414; WO 1996-US5070 19960412; US 1996-733225 19961017

AB US 6309671 B.UPAB: 20020301

NOVELTY - A powdered composition (A) comprises a **glassy** matrix and an active material. The composition has a **glass** transition temperature (Tg) of 35 - 200 deg. C. The stable dispersibility over time is characterized by a delivered dose efficiency of at least 30%, when the composition is stored at a storage temperature (Ts) of at least 10 deg. C lower than Tg over one month (preferably 3 months).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) maintaining dispersibility of the powdered composition over time involving:

(i) forming a solution which contains a solvent, a **glass former** capable of **forming** a **glassy** matrix and active material;

(ii) removing the solvent from the solution to form powder composition for inhalation; and

(iii) storing the composition for one month. The composition has a Tg of 22 - 200 deg. C and a storage temperature; and

(2) a powder composition comprising a first respirable powdered component containing (A) and a second nonrespirable powdered component containing powdered carrier.

ACTIVITY - Osteopathic; Cytostatic; Antidiabetic; Antianemic; Hemostatic; Immunostimulant; Neuroprotective; Gynecological; Analgesic; Anorectic; Uropathic; Hypotensive; Antirheumatic; Antiarthritic; Anti-HIV; Tranquilizer; Antilipemic; Antidiarrheic; Antianginal; Antimigraine; Virucide; Antiinflammatory; Antiasthmatic; Tuberculostatic; Antipyretic.

MECHANISM OF ACTION - None given.

USE - As a drug delivery system for treating pulmonary or systemic disease in a mammalian subject (claimed). The diseases include osteoporosis, Paget's disease, hypercalcemia, anemia, hemophilia B, neutropenia, transplant failure, short stature, renal failure, blood clotting, type I and type II diabetes, hepatitis B and C, multiple sclerosis, chronic granulomatous disease, renal cancer, prostate cancer, endometriosis, pain, ageing, obesity, gastrointestinal cancer, diabetes mellitus, diabetes insipidus, nocturnal enuresis, hypertension, amyotrophic lateral sclerosis, rheumatoid arthritis, cancer, immunodeficiency disease, acquired immune deficiency syndrome, thrombocytopenia, fungal disease, anxiety, hypercholesterolemia, peripheral neuropathies, refractory diarrhea, angina, cystic fibrosis, cytomegalovirus, Kaposi's sarcoma, hairy cell leukemia, migraine, hormone replacement therapy, lung transplant, respiratory syncytial virus, CMV, influenza and measles, chronic bronchitis, asthma, adult respiratory distress syndrome, fungal disease, tuberculosis, emphysema, pneumocystis carini pneumonia, bronchospasm, hay fever, bronchial asthma, pulmonary hypertension, lung cancer, pulmonary fibrosis, sarcoidosis and chronic obstructive pulmonary disease.

ADVANTAGE - The composition has stable dispersibility over time.

Dwg.0/13

L17 ANSWER 2 OF 24 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 2002-055629 [07] WPIDS

DNC C2002-015974

TI Cryopreservation of a cell in a dormant state, comprises microinjection of a sugar protective agent followed by treatment to induce the dormant state.

DC B04 D22

IN EROGLU, A; TONER, M; TOTH, T

PA (GAME-N) GAMETE TECHNOLOGIES INC; (GEHO) GEN HOSPITAL CORP

CYC 95

PI WO 2001087062 A2 20011122 (200207)* EN 54p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
ADT WO 2001087062 A2 WO 2001-US15748 20010516
PRAI US 2001-798327 20010302; US 2000-204877P 20000516
AB WO 200187062 A UPAB: 20020130
NOVELTY - Treating a living cell, comprising microinjecting a protective agent (comprising a sugar which does not permeate through a cell membrane and maintains the viability of the cell when stored in a dormant state) into the cytoplasm, treating the cell to cause it to enter a dormant state, and storing the cell in the dormant state, is new.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for culturing a cell in vitro, comprising incubating the cell in a hypertonic medium having an osmolarity greater than 300mosm.
USE - The method is useful for preserving biological material having a cell membrane.
ADVANTAGE - The method allows storage of the cells in a dormant state with recovery to an active state.
Dwg.0/19

L17 ANSWER 3 OF 24 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-482923 [52] WPIDS
DNC C2001-144662
TI Freeze **dried** oral composition useful for the treatment of migraine comprises at least one active substance in a form of a water soluble and water dispersible carrier material to form an open matrix network.
DC A96 B05
IN KHADGAPATHI, P; VENKATESWARA RAO, P
PA (NATC-N) NATCO PHARMA LTD
CYC 91
PI WO 2001039836 A1 20010607 (200152)* EN 27p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001020234 A 20010612 (200154)
ADT WO 2001039836 A1 WO 2000-IN78 20000825; AU 2001020234 A AU 2001-20234 20000825
FDT AU 2001020234 A Based on WO 200139836
PRAI IN 1999-1160 19991201
AB WO 200139836 A UPAB: 20010914
NOVELTY - A freeze **dried** oral composition comprises at least one active substance(s), a water soluble and water dispersible carrier material in an open matrix network, an optional coadministered active substance and/or other excepients.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for a process for preparation of a composition comprising: adding active substance to a solution/suspension of the water soluble or water dispersing carrier material to form the open matrix network; optionally adding other additives; transferring the resultant solution/suspension to a mold of the desired shape and a size of a final product; freezing the product in a freeze dryer at -50 - 10 deg. C; and re-**drying** at -40 - 90 deg. C under vacuum of 1 multiply 10-2 - 7.5 multiply 1-1 torr.

ACTIVITY - Antimigraine.
MECHANISM OF ACTION - None given.
USE - The invention is used for the treatment of migraine and migraine associated symptoms (claimed).
ADVANTAGE - The composition has: a rapid onset of action due to the rapid absorption of the active substance through oral mucosa, thus eliminates the need for parenteral administration of the medicament for crisis management; reduced dosage of the drugs as absorption through oral mucosa bypasses the first-pass metabolism and overcomes possible degradation in the gastro-intestinal tract; easy to administer to pediatric and geriatric patients; and as a medicament can be taken without water. Thus it can be administered in a non threatening, painless and simple way. The composition is suitable for patients who have difficulty in swallowing solid doses form.
Dwg.0/0

L17 ANSWER 4 OF 24 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-343328 [36] WPIDS
DNC C2001-106265
TI Aqueous suspension, used as a setting accelerator for a hydraulic binder, comprises a mixture of a polyol and an aluminum compound.
DC A93 L02
IN AMICHE, F; PRAT, E
PA (RHOD) RHODIA CHIM
CYC 94
PI WO 2001030721 A1 20010503 (200136)* FR 13p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
FR 2800061 A1 20010427 (200136)
AU 2000078016 A 20010508 (200149)
ADT WO 2001030721 A1 WO 2000-FR2884 20001016; FR 2800061 A1 FR 1999-13278 19991025; AU 2000078016 A AU 2000-78016 20001016
FDT AU 2000078016 A Based on WO 200130721
PRAI FR 1999-13278 19991025
AB WO 200130721 A UPAB: 20010628
NOVELTY - An aqueous suspension is formed of a polyol and aluminum compound mixture.
DETAILED DESCRIPTION - A novel aqueous suspension is formed from a mixture of one or more polyols and one or more aluminum compounds selected from salts and oxides, the aluminum compound concentration being at least 0.22 moles aluminum per 100 g suspension and the pH being not more than 5. An INDEPENDENT CLAIM is also included for an aluminum compound-based setting accelerator which has a setting time of not more than 6 min.
USE - The suspension is used, preferably in amount at least 1% by wt. of binder, as a setting accelerator for a hydraulic binder (claimed), especially cement in wet or **dry** spray mortars and concretes.
ADVANTAGE - The polyol addition provides improved suspension **stability** at high solids content and improved setting acceleration, while posing no safety or toxicity problems during use.
Dwg.0/0

L17 ANSWER 5 OF 24 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-191461 [19] WPIDS
DNN N2001-136058 DNC C2001-057365
TI Freeze-**drying**, e.g. for **stabilizing** preparation that is sensitive to hydrolysis and thermolabile or biological material, uses

vacuum-induced freezing before subliming frozen solvent.
DC B07 D13 D16 J08 Q76
IN KRAMER, M; SENNHENN, B
PA (FARB) BAYER AG
CYC 93
PI WO 2001009559 A1 20010208 (200119)* DE 28p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
DE 19936281 A1 20010215 (200119)
AU 2000066972 A 20010219 (200129)
ADT WO 2001009559 A1 WO 2000-EP7034 20000721; DE 19936281 A1 DE 1999-19936281 19990802; AU 2000066972 A AU 2000-66972 20000721
FDT AU 2000066972 A Based on WO 200109559
PRAI DE 1999-19936281 19990802
AB WO 200109559 A UPAB: 20010405
NOVELTY - Freeze-**drying** preparations (I) in a **drying** chamber by cooling and crystallizing the solvent (II) and sublimation of frozen (II) at reduced pressure is carried out in 3 phases, comprising:
(1) reducing the pressure in the **drying** chamber until visible crystallization of (II) occurs at a **drying** chamber temperature above the freezing point (Tf) of (I);
(2) reducing the temperature to Tf or below;
(3) subliming the frozen (II) by reduced pressure.
USE - Freeze-**drying** is useful for **stabilizing** preparations that are sensitive to hydrolysis and thermolabile and also biological materials, e.g. therapeutic sera, blood products, biologically active substances (hormones, vitamins, enzymes, pharmaceuticals), food and aromas.
ADVANTAGE - The usual processes inhibit release of gaseous solvent and suppress crystallization of dissolved contents, so that the products are (partly) amorphous. It can cause mechanical damage and loss and also collapse and thawing during **drying**, all of which are undesirable for pharmaceuticals and foods. The present process avoids these problems and gives a product that is easier to handle and has better mechanical **stability**.
Dwg.0/7

L17 ANSWER 6 OF 24 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-104805 [12] WPIDS
DNC C2001-030903
TI Preparation of free-flowing microparticles containing one or more active ingredients in **glassy** matrix, useful as food, feed, beverage or pharmaceutical additives, involves using multi-stage spray **drying** unit.
DC B07 D13
IN DE ROOS, K B; PERREN, M; SHERMAN, G A; DE ROSS, K B
PA (GIVA) GIVAUDAN-ROURE INT SA; (GIVA) GIVAUDAN SA
CYC 29
PI EP 1064856 A2 20010103 (200112)* EN 8p
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
CA 2313011 A1 20001230 (200112) EN
BR 2000002932 A 20010130 (200115)
ZA 2000003120 A 20010328 (200121) 17p
JP 2001072773 A 20010321 (200122) 8p
ADT EP 1064856 A2 EP 2000-113337 20000623; CA 2313011 A1 CA 2000-2313011

20000629; BR 2000002932 A BR 2000-2932 20000630; ZA 2000003120 A ZA 2000-3120 20000621; JP 2001072773 A JP 2000-196580 20000629
PRAI EP 1999-112446 19990630
AB EP 1064856 A UPAB: 20010302
NOVELTY - Free-flowing microparticles containing 1 or more active ingredients in a **glassy** matrix, which are dust-free during handling, are prepared using a multi-stage spray **drying** unit.

DETAILED DESCRIPTION - Preparation of free-flowing microparticles, dust-free during handling, at least 90 wt.% of the particles having diameter 100-400 mu m, containing 1 or more active ingredients in a **glassy** matrix, using a multi-stage spray **drying** unit comprises:

(a) forming an aqueous solution containing on solid basis (as wt.%) 40-70% of at least 1 low molecular weight carbohydrate and/or polyhydroxy compound, and 30-60% of at least 1 high molecular weight film forming agent, where the aqueous solution contains at least 50% of the agent(s);

(b) incorporating at least 1 active agent into the solution from (a) to form an emulsion or suspension containing (on aqueous basis) 1-35% active ingredient;

(c) spray **drying** the emulsion or suspension from (b) into a spray **drying** tower at an air inlet temperature of 100 180 deg. C and an air outlet temperature of 60-95 deg. C;

(d) transferring the surface **dried** semi-solid microparticles from (c), having water content 10-20% and particle size 10-200 mu m, and continuing **drying** and simultaneously agglomerating them at 25-55 (preferably 40-50) deg. C, resulting in solid, free-flowing particles with a **glassy** matrix having size at most 400 mu m and water content 2 6%;

(e) collecting the particles from (d), at least 90% of particles having size 100-400 mu m and water content 0.5-4%, and recycling particles of size less than 100 mu m from the fluid bed, either into the spray **drying** tower to allow growth of these particles by wetting with fresh sprayed-in emulsion or suspension of step (b), or to the upper part of the fluid bed to allow growth by agglomeration to 100-400 mu m.

INDEPENDENT CLAIMS are included for:

(1) the microcapsules produced, having bulk density at least 0.4 g/ml, having a **glassy** matrix of at least 1 mono-, di- or oligosaccharide and/or the corresponding alcohol containing entrapped active ingredient; and

(2) a method of flavoring a food or beverage product or feed supplement, comprising adding the encapsulated flavor in the form of microparticles prepared as above.

USE - The microparticles are useful as additives for food, feed, beverage or pharmaceutical products. Microparticles comprising encapsulated flavor may be compressed into tablets; added to a **dry** mix of food (e.g. instant soup, sauce or dessert); added to a **dry** beverage product (e.g. tea or instant coffee); or added to confectionery.

ADVANTAGE - Encapsulated flavors produced can be produced in a continuous process cycle with higher flavor loads than previous extruded flavors, resulting in lower production costs and costs in use. Lower temperatures are used than in standard spray **drying**, improving flavor retention, reducing thermal decomposition of sensitive flavors and enhancing shelf life **stability**. The process produces particles of low hygroscopicity by reducing the sugar content of the matrix without the need to increase the temperature during encapsulation as required with extrusion processes.

Dwg.0/0

L17 ANSWER 7 OF 24 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2000-431266 [37] WPIDS

DNC C2000-131043
TI Preparation of storage stable, amorphous, anhydrous disodium pamidronate useful for inhibiting bone absorption comprises adding sodium hydroxide solution to stirred slurry of pamidronic acid in water, filtering, freezing and lyophilizing.
DC B05
IN SHINAL, E C
PA (AESG-N) AESGEN INC
CYC 23
PI WO 2000034293 A1 20000615 (200037)* EN 16p
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP US
AU 2000020489 A 20000626 (200045)
US 6160165 A 20001212 (200067)
US 6268524 B1 20010731 (200146)
EP 1135397 A1 20010926 (200157) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
ADT WO 2000034293 A1 WO 1999-US29284 19991210; AU 2000020489 A AU 2000-20489 19991210; US 6160165 A US 1998-209153 19981210; US 6268524 B1 Cont of US 1998-209153 19981210, US 2000-639366 20000815; EP 1135397 A1 EP 1999-964198 19991210, WO 1999-US29284 19991210
FDT AU 2000020489 A Based on WO 200034293; EP 1135397 A1 Based on WO 200034293
PRAI US 1999-456460 19991208; US 1998-209153 19981210; US 1999-414401 19991007; US 2000-639366 20000815
AB WO 200034293 A UPAB: 20000807
NOVELTY - Preparation of amorphous, anhydrous disodium pamidronate comprises:
(a) preparing a stirred slurry of pamidronic acid in water;
(b) adding aqueous solution of sodium hydroxide in a 2:1 molar ratio of sodium hydroxide to pamidronic acid to give a clear solution having a pH of about 6.5;
(c) filtering the solution; and
(d) freezing and lyophilizing.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(i) disodium pamidronate prepared by the above process;
(ii) a method for preparing a therapeutic aqueous disodium pamidronate solution comprising steps (a) and (b) as above and (c) packaging the solution in sealed containers to give liquid unit dosage forms of pamidronate;
(iii) a unit dose form comprising disodium pamidronate solution prepared as above; and
(iv) a capsule, intranasal spray dispenser, vial or ampoule comprising the above unit dosage form.
ACTIVITY - Osteopathic.
USE - For preparing amorphous, anhydrous disodium pamidronate useful for inhibiting bone absorption, to treat moderate or severe hypercalcemia associated with malignancy with or without bone metastases.
ADVANTAGE - The process is simple and gives dosage forms that are storage stable.
Dwg.0/0

L17 ANSWER 8 OF 24 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2000-399647 [34] WPIDS
DNC C2000-120647
TI New adenovirus formulations containing excipients for storage **stability**, useful for gene therapy for treating e.g. viral disease, genetic disease or malignancies.
DC A96 B04 B07 D16
IN WU, Z; ZHANG, S
PA (INTR-N) INTROGEN THERAPEUTICS INC

CYC 91
PI WO 2000029024 A1 20000525 (200034)* EN 121p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000017296 A 20000605 (200042)
EP 1133316 A1 20010919 (200155) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
ADT WO 2000029024 A1 WO 1999-US27177 19991116; AU 2000017296 A AU 2000-17296 19991116; EP 1133316 A1 EP 1999-960405 19991116, WO 1999-US27177 19991116
FDT AU 2000017296 A Based on WO 200029024; EP 1133316 A1 Based on WO 200029024
PRAI US 1999-133116P 19990507; US 1998-108606P 19981116
AB WO 200029024 A UPAB: 20000718
NOVELTY - A novel pharmaceutical adenovirus (Ad) composition comprises Ad particles and pharmaceutical excipients, the excipients including a bulking agent and one or more protectants, where the excipients are included to provide an Ad composition that is storage stable.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) an aqueous pharmaceutical Ad composition comprising a polyol to promote the maintenance of Ad infectivity;
(2) a method for preparation of a long-term, storage stable Ad formulation comprising:
(a) providing Ad and combining the Ad with a solution comprising a buffer, a bulking agent, a cryoprotectant and a lyoprotectant; and
(b) lyophilizing the solution; where lyophilization of the solution produces a freeze-**dried** cake of the Ad formulation that retains high infectivity and low residual moisture;
(3) a method for the preparation of a long-term storage stable Ad liquid formulation comprising providing Ad and combining the Ad with a solution comprising a buffer and a polyol, whereby the Ad liquid formulation retains high infectivity.
USE - The Ad compositions can be used for gene therapy treatments of viral disease, genetic disease or malignancies.
ADVANTAGE - The addition of a polyol to Ad compositions can maintain an infectivity of about 70-99.9% PFU/ml of the starting infectivity when stored for 6 months at 4 deg. C. The methods can provide highly purified lyophilized and liquid Ad compositions with long-term storage **stability**.
Dwg.0/9

L17 ANSWER 9 OF 24 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2000-376040 [32] WPIDS
DNC C2000-113595
TI Solid delivery systems for aroma ingredients comprising extrusion formed matrix.
DC B07 D13 D21 E13
IN BENCZEDI, D; BOUQUERAND, P; FIRMENICH, A; MCIVER, R C; MUTKA, J R; PALMER, C A
PA (FIRM) FIRMENICH SA; (BENC-I) BENCZEDI D; (BOUQ-I) BOUQUERAND P; (FIRM-I) FIRMENICH A; (MCIV-I) MCIVER R C; (MUTK-I) MUTKA J R; (PALM-I) PALMER C A
CYC 26
PI WO 2000025606 A1 20000511 (200032)* EN 38p
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: BR CA CN ID IN JP US
EP 1124443 A1 20010822 (200149) EN

R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
BR 9915007 A 20010807 (200152)
US 2001038879 A1 20011108 (200171)
ADT WO 2000025606 A1 WO 1999-IB1777 19991103; EP 1124443 A1 EP 1999-951043 19991103, WO 1999-IB1777 19991103; BR 9915007 A BR 1999-15007 19991103, WO 1999-IB1777 19991103; US 2001038879 A1 CIP of US 1998-185536 19981104, Cont of WO 1999-IB1777 19991103, US 2001-847906 20010503
FDT EP 1124443 A1 Based on WO 200025606; BR 9915007 A Based on WO 200025606
PRAI IN 1998-3309 19981109; US 1998-185536 19981104
AB WO 200025606 A UPAB: 20000706
NOVELTY - A solid delivery system for the release of aroma ingredients comprises an extrusion formed matrix containing a hydrophilic aroma material.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for the preparation of a stable melt-based, extruded aroma delivery system comprising:

(a) combining and blending a hydrophilic aroma with an extrudable matrix material, an emulsifier and optionally a plasticizer under temperature and stirring conditions useful to produce a uniform melt;

(b) extruding the molten mass through a die;

(c) chopping, cutting, grinding or pulverizing the mass obtained either as it exits the die or after having cooled the molten mass; and

(d) optionally **drying**.

USE - The delivery system can be used to impart, improve, enhance or modify the odour or taste of a consumer product such as a foodstuff, beverage, edible composition, pharmaceutical composition, pharmaceutical composition, chewing-gum or toothpaste (claimed). The hydrophilic flavoring ingredients can replace, partially or totally, the sugar component present in maltodextrin-based matrices, thus providing non-cariogenic flavoring compositions for use in low sugar or sugar-free foods. The extruded solids can be used to impart or modify the organoleptic properties of a great variety of edible products. They enhance the typical organoleptic effect of the corresponding unextruded hydrophilic flavor material and they are more effective than the latter in the coverage and masking of any off-notes present in the food or beverage, such as the bitter notes of coffee- and tea-based beverages, the sour notes of soya-based edible products of at certain cereal or flour-based foods, or metallic notes detectable in mint flavored sweets and candies.

ADVANTAGE - The high content in hydrophilic active ingredients renders the delivery systems cost-effective. The granulated products are far easier to handle, as they produce no significant amounts of dust when processed in the consumer products into which they are incorporated.
Dwg.0/0

L17 ANSWER 10 OF 24 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 1999-573914 [49] WPIDS
DNC C1999-167604
TI Rheologically and microbiologically stable pigment and/or filler dispersion useful in manufacture of paper, paints and varnishes, inks, adhesives, detergents, textiles and leather, plastics and rubber, films, etc..
DC A60 D18 D21 D25 E13 E17 E19 F06 F09 G02 G03 L02
IN BAUDELLE, R; GOSSET, S; LEFER, P; MERLE DU BOURG, R; DU BOURG, R M
PA (BAUD-I) BAUDELLE R; (GOSS-I) GOSSET S; (LEFE-I) LEFER P; (DBOU-I) MERLE DU BOURG R; (ROQF) ROQUETTE FRERES SA
CYC 28
PI EP 950697 A1 19991020 (199949)* FR 9p
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
FR 2777478 A1 19991022 (199951)

NO 9901819 A 19991018 (199953)
CA 2269306 A1 19991017 (200013) FR
US 6267812 B1 20010731 (200146)
ADT EP 950697 A1 EP 1999-400909 19990414; FR 2777478 A1 FR 1998-4837 19980417; NO 9901819 A NO 1999-1819 19990416; CA 2269306 A1 CA 1999-2269306 19990415; US 6267812 B1 US 1999-292251 19990415
PRAI FR 1998-4837 19980417
AB EP 950697 A UPAB: 19991124
NOVELTY - Pigment and/or filler dispersion with a Brookfield viscosity (20 deg. C, 20 rpm) of 100-4000 mPa.s and a viscosity instability index of less than 35% (percentage decrease in viscosity after storage in sealed **glass** jars at 20-22 deg. C for 7 days) contains a saccharide composition including at least 30 wt.% of one or more hydrogenated mono- and/or disaccharides.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for the use of optionally hydrogenated oxidized saccharides as dispersants in pigment and/or filler compositions

USE - The dispersions are useful in the manufacture of paper, paints and varnishes, inks, adhesives, detergents, textiles and leather, plastics and rubber, films, ceramics, enamels, building materials and cosmetics.

ADVANTAGE - The dispersions have good rheological and microbiological storage **stability**, have little tendency to form deposits in processing, storage and transport containers, are readily pumpable, and can have high solids contents.

Dwg.0/0

L17 ANSWER 11 OF 24 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 1999-561869 [47] WPIDS
DNC C1999-163800
TI Method of **drying**, without damage, compounds subject to **deactivation** on **drying** or their mixtures such as proteins, polysaccharides or nucleic acids.
DC A14 A96 A97 B04 D13 D16
IN DE CASTRO, A G; ROSER, B J
PA (CAMB-N) CAMBRIDGE BIOSTABILITY LTD; (RONA-I) RONAI P
CYC 87
PI WO 9947174 A1 19990923 (199947)* EN 26p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW
AU 9929451 A 19991011 (200008)
EP 1071465 A1 20010131 (200108) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
ADT WO 9947174 A1 WO 1999-GB820 19990317; AU 9929451 A AU 1999-29451 19990317; EP 1071465 A1 EP 1999-910516 19990317, WO 1999-GB820 19990317
FDT AU 9929451 A Based on WO 9947174; EP 1071465 A1 Based on WO 9947174
PRAI GB 1998-20689 19980923; GB 1998-5699 19980318
AB WO 9947174 A UPAB: 19991116
NOVELTY - Method of **drying**, without damage, compounds subject to **deactivation** on **drying** or their mixtures by subjecting aqueous system containing compounds to **drying** in presence of one or more monosaccharide **sugar alcohols** and at least one additive that is a **glass former** or **glass-formation facilitator** whereby the compounds solidify from solution as amorphous **glass** rather than by **forming** crystals.

USE - The method is used to **dry**, without damage, compounds

subject to **deactivation** on **drying** or their mixtures such as proteins, polysaccharides, nucleic acids, enzyme, serum, serum complement, antibody or antigen (free or coupled to support), nucleic acid, fluorescent protein or vaccine component (claimed). The method is also used to **stabilize** sensitive products.

ADVANTAGE - The method uses regulatory authority approved reagents for oral and parenteral formulations that are low cost, chemically inert and with exceptional **stability**, high purity and safety. The method uses mixtures of substances that are additive so that formulations contain sub-threshold doses of each additive alone, produces high-quality product, with improved flexibility of formulation and product presentation and products are chemically inert and non-reactive such that the entrapped products are stable at room temperature, without requiring refrigeration.

DESCRIPTION OF DRAWING(S) - Percentage recovery of alkaline phosphatase activity after vacuum **drying** in either trehalose or test formulation containing **mannitol**, inositol, galactitol and Byco C (RTM: degraded gelatin) C followed by storage at 37 deg. C or 50 deg. C for up to 6 weeks.

Dwg.3/8

L17 ANSWER 12 OF 24 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 1997-424767 [39] WPIDS
CR 1997-087022 [08]; 1997-448320 [41]
DNC C1997-135903
TI Freeze-**dried** vesicular ultrasound contrast agents with improved thermal **stability** - comprises freeze-**drying** **stabiliser**, such as sucrose, and are also useful in e.g. magnetic resonance imaging, X-ray, and magnetographic imaging.
DC A96 B05 P31 P73
IN BRAENDEN, J U; FAHLVIK, A K; GULLIKSEN, P H; BRAENDEN, J; DUGSTAD, H; KLAVENESS, J; RONGVED, P; SKURTVEIT, R; SWAERD-NORDMO, M; SWAERDNORDMO, M; BRENDEN, J
PA (NYCO-N) NYCOMED IMAGING AS; (COCK-I) COCKBAIN J
CYC 77
PI WO 9729782 A1 19970821 (199739)* EN 26p
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN YU
AU 9718051 A 19970902 (199751)
ZA 9701408 A 19971231 (199807) 52p
BR 1100844 A3 19980512 (199828)
NO 9803584 A 19981016 (199901)
EP 885016 A1 19981223 (199904) EN
R: AL AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV MC NL PT RO SE SI
CZ 9802626 A3 19990317 (199917)
CN 1213971 A 19990414 (199933)
HU 9900812 A2 19990728 (199936)
NZ 331372 A 20000128 (200015)
JP 2000506122 W 20000523 (200033) 24p
AU 722735 B 20000810 (200043)
KR 99082670 A 19991125 (200055)
US 6165442 A 20001226 (200103)
US 6217850 B1 20010417 (200123)
MX 9806655 A1 20000601 (200133)
ADT WO 9729782 A1 WO 1997-GB458 19970219; AU 9718051 A AU 1997-18051 19970219; ZA 9701408 A ZA 1997-1408 19970219; BR 1100844 A3 BR 1997-1100844 19970512; NO 9803584 A WO 1997-GB458 19970219, NO 1998-3584 19980805; EP

885016 A1 EP 1997-903507 19970219, WO 1997-GB458 19970219; CZ 9802626 A3 WO 1997-GB458 19970219, CZ 1998-2626 19970219; CN 1213971 A CN 1997-193181 19970219; HU 9900812 A2 WO 1997-GB458 19970219, HU 1999-812 19970219; NZ 331372 A NZ 1997-331372 19970219, WO 1997-GB458 19970219; JP 2000506122 W JP 1997-529130 19970219, WO 1997-GB458 19970219; AU 722735 B AU 1997-18051 19970219; KR 99082670 A WO 1997-GB458 19970219, KR 1998-706416 19980818; US 6165442 A Cont of WO 1997-GB458 19970219, Provisional US 1997-46652P 19970516, US 1998-78711 19980514; US 6217850 B1 Cont of WO 1996-GB1361 19960607, Cont of US 1997-776647 19970207, US 1998-84105 19980526; MX 9806655 A1 MX 1998-6655 19980817

FDT AU 9718051 A Based on WO 9729782; EP 885016 A1 Based on WO 9729782; CZ 9802626 A3 Based on WO 9729782; HU 9900812 A2 Based on WO 9729782; NZ 331372 A Based on WO 9729782; JP 2000506122 W Based on WO 9729782; AU 722735 B Previous Publ. AU 9718051, Based on WO 9729782; KR 99082670 A Based on WO 9729782

PRAI GB 1996-24919 19961129; GB 1996-3466 19960219; GB 1996-11894 19960607; GB 1995-11488 19950607

AB WO 9729782 A UPAB: 20010615

Freeze-**dried** vesicles comprise ultrasound contrast agents containing a freeze-**drying stabiliser**, and are thermally stable at above 20 deg. C. Also claimed are: (a) freeze-**dried** vesicles comprising ultrasound contrast agents containing a freeze-**drying stabiliser**, with a Tg (**glass** transition temperature) value > 20 deg. C; (b) an ultrasound contrast medium comprising an aqueous carrier, an echogenic vesicular ultrasound contrast agent and at least one freeze-**drying stabiliser** with a Tg of at least 20 deg. c and a Tg' (**glass** transition temperature of maximally freeze-concentrated pure aqueous solution of the material) value of - 37 deg. C or above; and (c) a process for the storage or transportation of the above vesicles, without the use of cooling.

USE - The vesicles are used as ultrasound contrast agents and in other diagnostic imaging modalities (claimed) e.g. MRI, X-ray SPECT, PET and magnetographic imaging.

ADVANTAGE - The **stability** eradicates the need for temperature control and the product may be supplied to hospitals and physicians for on site formulation, without the use of special storage facilities. The lyophilised products are stable for several months under ambient conditions and the reconstituted vesicle dispersions generated are stable for up to at least 12 months, permitting flexibility as to when the **dried** product is reconstituted prior to injection. Use of the **stabilisers** during freeze-**drying** shortens freeze-**drying** cycles since the compositions have higher **glass** temperatures than the corresponding compositions containing cryoprotectants such as glucose or **mannitol**. The vesicular contrast agents enhance the ability of the vesicles to retain commonly used halocarbon gases and gas precursors.

Dwg.0/0

L17 ANSWER 13 OF 24 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 1996-310867 [32] WPIDS

CR 1996-310868 [32]; 1997-447383 [41]

DNC C1996-099293

TI Sugar-free boiled sweets contg. polyol and with high water content - are highly stable and do not cause dental caries.

DC D13

IN RIBADEAU-DUMAS, G; SERPELLONI, M

PA (ROQF) ROQUETTE FRERES SA; (FRER-I) FRERES R

CYC 28

PI EP 720819 A2 19960710 (199632)* FR 6p

R: AT BE CH DE DK ES FR GB GR IE IT LI NL PT SE

FR 2728436	A1	19960628	(199633)	23p
AU 9540647	A	19960704	(199634)	
NO 9505266	A	19960627	(199635)	
CZ 9503388	A3	19960717	(199637)	
FI 9506166	A	19960627	(199640)	
FI 9506167	A	19960627	(199640)	
CA 2165837	A	19960627	(199642)	
CA 2165838	A	19960627	(199642)	
JP 08228688	A	19960910	(199646)	6p
ZA 9510791	A	19970226	(199714)	21p
US 5629042	A	19970513	(199725)	5p
HU 75897	T	19970528	(199805)	
HU 75902	T	19970528	(199805)	
BR 9506065	A	19971223	(199806)	
HU 214445	B	19980330	(199823)	
NZ 280718	A	19980728	(199836)	
AU 703326	B	19990325	(199924)	
KR 163252	B1	19981116	(200030)	
MX 192731	B	19990721	(200061)	
MX 194031	B	19991111	(200106)	

ADT EP 720819 A2 EP 1995-402929 19951222; FR 2728436 A1 FR 1994-15648 19941226; AU 9540647 A AU 1995-40647 19951222; NO 9505266 A NO 1995-5266 19951222; CZ 9503388 A3 CZ 1995-3388 19951220; FI 9506166 A FI 1995-6166 19951221; FI 9506167 A FI 1995-6167 19951221; CA 2165837 A CA 1995-2165837 19951220; CA 2165838 A CA 1995-2165838 19951220; JP 08228688 A JP 1995-339020 19951226; ZA 9510791 A ZA 1995-10791 19951219; US 5629042 A US 1995-470462 19950606; HU 75897 T HU 1995-3787 19951222; HU 75902 T HU 1995-3789 19951222; BR 9506065 A BR 1995-6065 19951222; HU 214445 B HU 1995-3787 19951222; NZ 280718 A NZ 1995-280718 19951220; AU 703326 B AU 1995-40647 19951222; KR 163252 B1 KR 1995-54570 19951222; MX 192731 B MX 1996-79 19960103; MX 194031 B MX 1996-78 19960103

FDT HU 214445 B Previous Publ. HU 75897; AU 703326 B Previous Publ. AU 9540647

PRAI US 1995-470462 19950606; FR 1994-15648 19941226; US 1995-470464 19950606

AB EP 720819 A UPAB: 20010126

Sugar-free boiled sweets comprising, w.r.t. **dry** matter, 5-100% of at least one polyol which crystallises in water, have a water content of > 3% and a **glass** transition temp. (measured at a 3.2% water content) of at least 38 deg. C. Also claimed is the above prod. where the **glass** transition temp. is measured at the effective water content. Also claimed is the prepn. of stable sugar-free boiled sweets comprising: (i) prepn. of a syrup contg. 5-100% of a crystallisable polyol selected from maltitol, erythritol, isomalt, **mannitol**, sorbitol, xylitol or lactitol, such that it confers a 38 deg. C **glass** transition temp. (measured at 3.2% water content) to the sweets; (ii) boiling the sugar to facilitate vitrification of a the cooked mass which contains more than 3 (pref. 3.5 %) water.

ADVANTAGE - The prod. is highly stable, does not become sticky or white and opaque during storage and is not hygroscopic. It does not cause dental caries, neither does not lose its shape at normal temp. and retains its organoleptic properties, but avoids a high calorie content. Mfr. takes place at lower temperatures, giving a pale colour and reducing prodn. costs.

Dwg.0/0

L17 ANSWER 14 OF 24 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 1994-040031 [05] WPIDS

DNC C1994-018133

TI **Stabilised** compsns. of calcitonin(s) - comprise lyophilisate(s) comprising sugars and sodium chloride as **stabilisers**.

DC B04
PA (ASAH) ASAHI CHEM IND CO LTD
CYC 1
PI JP 05345729 A 19931227 (199405)* 6p
ADT JP 05345729 A JP 1992-154594 19920615
PRAI JP 1992-154594 19920615
AB JP 05345729 A UPAB: 19940315
Stabilised compsns. contg. calcitonin as effective components are lyophilisate comprising 1 wt. part of sugars and 1/100-1/4 wt. part of sodium chloride.

The sugars are one or more selected from **mannitol**, glucose, sorbitol, inositol, xylitol, galactose, fructose, sucrose, maltose, lactose, trehalose, dextran, and cyclodextrin.

Stabilisation of calcitonins comprises dissolution in aq. media of mixts. contg. calcitonins as effective components and also 1 wt. part of sugars and 1/100-1/4 wt. part of sodium chloride followed by lyophilisation.

USE/ADVANTAGE - The compsns. in which sodium chloride and sugars are employed in combination show the remaining activities of 85% or more. Single application of the sugars cause decrease in **stability** at 40 deg.C in the course of 3 months. Also, the single or excessive application of sodium chloride gives unfavourable shrinking in the process of lyophilisation and also a decrease in **stability**.

In an example, calcitonin (1.5mg, 6000 units/mg), 500 mg sucrose, and 50 mg NaCl were dissolved in 50 ml sterilised water. After sterilised filtration, each 0.5 ml of the filtrate was placed in **glass** vials under nitrogen atoms. to give a **dry** prepn. dissolved in use. The remaining ratio of calcitonin was 96% after 3-month storage at 40 deg.C. Without the addn. of NaCl, the ratio was as low as 77% and shrinking was observed on the prepn..
Dwg.0/0

L17 ANSWER 15 OF 24 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 1992-417619 [51] WPIDS
DNC C1992-185238
TI Cooked sugarless sweet meat - prepd. from hydrogenated starch hydrolysate, xylitol, saccharide polymers, isomaltulose etc..
DC D13
IN MENTINK, L; SERPELLONI, M
PA (ROQF) ROQUETTE FRERES SA
CYC 26
PI EP 518770 A1 19921216 (199251)* FR 11p
R: AT BE CH DE DK ES FR GB GR IT LI LU MC NL PT SE
AU 9218211 A 19921217 (199306)
FR 2677524 A1 19921218 (199307) 23p
NO 9202292 A 19921215 (199307)
CA 2071168 A 19921215 (199310)
FI 9202723 A 19921215 (199310)
ZA 9204311 A 19930825 (199339) 23p
US 5314701 A 19940524 (199420) 7p
JP 06197697 A 19940719 (199433) 8p
AU 653822 B 19941013 (199442)
IL 102140 A 19941128 (199504)
EP 518770 B1 19950719 (199533) FR 13p
R: AT BE CH DE DK ES FR GB GR IT LI LU MC NL PT SE
DE 69203542 E 19950824 (199539)
ES 2077997 T3 19951201 (199604)
IE 67881 B 19960501 (199629)
NO 304214 B1 19981116 (199901)
KR 231258 B1 19991115 (200111)

FI 107225 B1 20010629 (200140)
ADT EP 518770 A1 EP 1992-401622 19920612; AU 9218211 A AU 1992-18211 19920612; FR 2677524 A1 FR 1991-7330 19910614; NO 9202292 A NO 1992-2292 19920611; CA 2071168 A CA 1992-2071168 19920612; FI 9202723 A FI 1992-2723 19920612; ZA 9204311 A ZA 1992-4311 19920612; US 5314701 A US 1992-896004 19920611; JP 06197697 A JP 1992-155392 19920615; AU 653822 B AU 1992-18211 19920612; IL 102140 A IL 1992-102140 19920609; EP 518770 B1 EP 1992-401622 19920612; DE 69203542 E DE 1992-603542 19920612, EP 1992-401622 19920612; ES 2077997 T3 EP 1992-401622 19920612; IE 67881 B IE 1992-1929 19920701; NO 304214 B1 NO 1992-2292 19920611; KR 231258 B1 KR 1992-10291 19920613; FI 107225 B1 FI 1992-2723 19920612
FDT AU 653822 B Previous Publ. AU 9218211; DE 69203542 E Based on EP 518770; ES 2077997 T3 Based on EP 518770; NO 304214 B1 Previous Publ. NO 9202292; FI 107225 B1 Previous Publ. FI 9202723
PRAI FR 1991-7330 19910614
AB EP 518770 A UPAB: 19931116
A cooked sugarless sweetmeat has a multilayer structure in which the outer layer comprises at most 35%, pref. at most 25% by wt. of the sweetmeat and consists of at least 2 components A and B.

A is present at 5-92wt.% (w.r.t. solids) and consists of one or more of the following:- hydrogenated starch hydrolysates (HSH), xylitol and hypocaloric saccharide polymers; B is present at 8-95wt.% and has a solubility in water of less than 60g per 100g water at 20 deg.C and a hygroscopicity in crystallised form such that it absorbs less than 3% of its weight in an atmosphere having a relative humidity less than or equal to 85%, at 20 deg.C.

ADVANTAGE - Addn. of A to B prevents crystallisation of B during prodn., partic. at the time of cooking and avoids graining during storage. The prod. also has good heat **stability** at least equivalent to HSH/isomalt sweetmeat of prior art. The temp. at which cold flow occurs with the sweetmeat of the invention is markedly higher than that of sweetmeats having homogeneous monoblock structure.
Dwg.0/0

L17 ANSWER 16 OF 24 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 1991-105697 [15] WPIDS
DNC C1991-045482
TI Drugs for inhibiting the growth of aids virus - comprises natural prod. e.g. biliverine contg. tetra pyrrole deriv. taken orally as tablet, granule or powder.
DC A96 B03
PA (NIHA-N) NIPPON HAM KK
CYC 1
PI JP 03047166 A 19910228 (199115)* 5p
JP 2933229 B2 19990809 (199937) 4p
ADT JP 03047166 A JP 1989-190326 19890721; JP 2933229 B2 JP 1989-190326 19890721
FDT JP 2933229 B2 Previous Publ. JP 03047166
PRAI JP 1989-91179 19890411; JP 1989-190326 19890721
AB JP 03047166 A UPAB: 19930928
Title drugs contg. as active component a tetrapyrrole deriv. of formula (I) or its salt are new, wherein R1 and R2 = OH or substd. OH (e.g. acyloxy, alkoxy); the tetrapyrrole nuclei may be substitd. at the 2, 3, 7, 8, 12, 13, 17 and 18 positions.

(I) are isolated from natural prods., e.g. bile pigment; particularly useful one is biliverdin (VN). Pref. the oral prepns. include tablets, granules, powder, capsules, soln., suspension, emulsion, and freeze-**dried** prepn. which may be prepd. with non-toxic carriers, e.g. glucose, lactose, sucrose, starch, **mannitol**, dextrin, fatty acid glyceride, polyethylene glycol, hydroxyethyl starch, ethylene glycol,

polyoxyethylenesorbitan fatty acid ester, amino acids, gelatin, albumin, water, physiological saline. If necessary conventional additives e.g. **stabiliser**, wetting agent, emulsifying agent, binder, isotonic agent, may be added.

USE/ADVANTAGE - (I) specifically inhibit the growth of HIV or of cells infected by HIV. (I) may be administered orally at a daily dose of 1-300 mg/kg. Also applicable as injection or rectal preps. In an example VN (20g) was dispersed in 50 ml 5 w/v% aq. polyoxyethylene polyoxypropylene glycol and crushed with **glass** beads. The resulting suspension (50 ml) was mixed with 30 g sucrose fatty acid ester, and the mixt. was freezed with **dry** ice MeOH and **dried** to yield a freeze **dried** prepn. @(5pp Dwg.No.0/0)@

L17 ANSWER 17 OF 24 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 1987-067616 [10] WPIDS
DNC C1987-028054
TI Soft capsule coat contg. **mannitol** - with no adhesion during high temp. storage.
DC B07 D21
PA (NISS-N) NISSHIN KAGAKU KK
CYC 1
PI JP 62019516 A 19870128 (198710)* 4p
JP 04073409 B 19921120 (199251) 4p
ADT JP 62019516 A JP 1985-157384 19850717; JP 04073409 B JP 1985-157384 19850717
FDT JP 04073409 B Based on JP 62019516
PRAI JP 1985-157384 19850717
AB JP 62019516 A UPAB: 19930922
New soft coat is prepd. by blending 4-10 wt.% of D-**mannitol** with gelatin. The surface of the coat is roughened.

A mixt. of 40-60% gelatin, 10-30% glycerin, 2-15% **mannitol**, and 35-55% water is left for a certain time to swell. After dissolved by heating, the mixt. is extended, coated, solidified, and **dried** to yield the coat. The roughening is industrially done by spreading cloth in a drier.

USE/ADVANTAGE - The coat does not adhere to itself or to the vessel during high-temp. storage. Its high rigidity allows prepn. of a capsule with thin coating. Its decay time is short and changes little with time. The rough, opaque surface gives a beautiful, unique appearance like frosted **glass** and **facilitates** coating, e.g. with waxes. It is available for oral drugs or suppositories, cosmetics, bath agents, etc..
0/0

L17 ANSWER 18 OF 24 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 1986-319025 [49] WPIDS
DNC C1986-138166
TI Gel resistant aq. compsn. contg. **glass** micro-bubbles - and high mol. and low mol. poly-hydroxy cpds., and **glass** bubble coated with low mol. poly-hydroxy cpd..
DC A93 E19 G04
IN MONTGOMERY, R L
PA (MINN) MINNESOTA MINING & MFG CO
CYC 3
PI AU 8654416 A 19861023 (198649)* 15p
US 4629751 A 19861216 (198701)
CA 1300793 C 19920512 (199225)
ADT AU 8654416 A AU 1986-54416 19860307; US 4629751 A US 1985-724460 19850418; CA 1300793 C CA 1986-503377 19860305
PRAI US 1985-724460 19850418

AB AU 8654416 A UPAB: 19930922
A gel-resistant compsn. contains (a) **glass** micro-bubbles, (b) a high mol. wt. polyhydroxy cpd. binder, (c) water, and (d) a low mol. wt. polyhydroxy cpd. in which at least 2 OH are attached to C atoms sepd. by at least 1 C atom. Pref. **glass** bubbles are **formed** from a compsn. including trivalent B. Partic., a **glass** bubble for incorporation in an aq. soln. or emulsion of a high mol. poly-hydroxy cpd. comprises a borate-contg. **glass** bubble coated with a low mol. wt. polyhydroxy cpd. (claimed). Pref. (b) is polyvinyl alcohol. (d) is alpha-D-galacturonic acid, glucuronic acid, sorbitol, D-glucose, D+ **mannitol**, D-ribose, glyceraldehyde, pentaerythritol, 1,2,6-trihydroxy-hexane, gluconic acid and mannose.

In an example, compsn. contg. 800 pts. wt. of 5 wt. % aq. soln. of polyvinyl alcohol, 15 pts. ethylene glycol, 5.5 pts. 'Nuosept' 95 (RTM : preservative), 18 pts. attapulgus clay, 244 pts. ground CaCO3, 77 pts. talc, 36 pts. mica powder, 5 pts. 'Cellocize' TJC 500 (RTM : thixotropic agent), 12 pts. sorbitol, and 130 pts. '3M C15/250' (RTM : **glass** bubbles) showed no signs of gelation even after standing for several days. When applied to gypsum board the compsn. adhered well to seam tape, did not sag on vertical surfaces, **dried** at the normal rate, and could be sanded after **drying**.

USE/ADVANTAGE - Patching or repairing plaster, or gypsum board panels (claimed). The compsn. can be used without gelling on plaster wallboard which has been rendered fire-retardant by H3BO3.
0/0

L17 ANSWER 19 OF 24 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 1986-261563 [40] WPIDS
DNN N1986-195486 DNC C1986-113157
TI **Stabilised** immobilised antibody - prepd. by treating immobilised antibody with aq. soln. contg. cane sugar and/or **mannitol** as projective agent and the **drying** after treatment.
DC B04 S03
PA (FUJI) FUJISAWA PHARM CO LTD
CYC 1
PI JP 61189454 A 19860823 (198640)* 6p
ADT JP 61189454 A JP 1985-31138 19850218
PRAI JP 1985-31138 19850218
AB JP 61189454 A UPAB: 19930922
New **stabilised** immobilised antibody where immobilised carrier made insoluble by binding antibody used for immunochemical assay is treated with aq. soln. contg. cane sugar and/or **mannitol** as protective agent, and **dried** after treatment.

Solid phase carrier used in this invention is not specifically limited, but all solid phase carriers used for immunochemical assays may be used. Pref. carrier in disk or bead or tube shape made of plastic, **glass** or paper is used; however, plastic-make micro plate is most pref.

USE/ADVANTAGE - **Stabilised** immobilised antibody can be stored for long time without damage to immune activity in case of immobilised antibody used for immunochemical assay, and used in medical treatment field, e.g. diagnosis of illnesses, etc. Immobilised antibody of this invention can be stably kept for long time free from damage to activity of antibody even if it is stored in **drying** conditions where activity of antibody will ordinarily be deteriorated, and not only at low temp. but also at room temp. Thus, kinds used for immunochemical assay of vital trace components using immobilised antibody of this invention is more effective because it can be simple in preservation, transportation, handling, etc.
0/0

L17 ANSWER 20 OF 24 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 1985-084149 [14] WPIDS
DNN N1985-062772 DNC C1985-036765
TI **Stabilising** immuno-active substance fixed to insol. carrier - by immersing in soln. contg. **sugar**, protein and/or polyfunctional lower **alcohol**.
DC A96 B04
IN GOTO, M; HAMAGUCHI, Y; KOBATAKE, S; SAKATA, Y
PA (WAKP) WAKO PURE CHEM IND LTD
CYC 14
PI JP 60035263 A 19850223 (198514)* 13p
EP 140489 A 19850508 (198519) EN
R: AT BE CH DE FR GB IT LI LU NL SE
EP 140489 B 19890419 (198916) EN
R: AT BE CH DE FR GB IT LI LU NL SE
DE 3477844 G 19890524 (198922)
JP 05041946 B 19930625 (199328) 8p
US 5273908 A 19931228 (199401) 7p
ADT JP 60035263 A JP 1983-144201 19830805; EP 140489 A EP 1984-305286 19840803; JP 05041946 B JP 1983-144201 19830805; US 5273908 A Cont of US 1984-638086 19840806, Cont of US 1987-38490 19870413, US 1991-659476 19910225
FDT JP 05041946 B Based on JP 60035263
PRAI JP 1983-144201 19830805
AB JP 60035263 A UPAB: 19930925
Method comprises immersing the fixed immunoactive substance in a soln. contg. at least one of sugars, proteins and polyfunctional lower alcohols; and reagents for immunoassay comprising the **stabilised** immunoactive substance as main component.
Specifically claimed are cases in which said carrier is an inorganic substance (e.g., **glass**, silica gel and metal oxides), in which said carrier is a synthetic polymer (e.g., polystyrene, PVC, polypropylene and polyethylene), and in which the fixed immunoactive substance is an antigen or an antibody.
0/0

L17 ANSWER 21 OF 24 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 1980-90627C [51] WPIDS
TI Finely divided copper on silica hydrogenation catalyst - prepd. by coprecipitation of copper and **silicate** salts at controlled ph.
DC E19 J04
IN RUDDLESDEN, J F; STEWART, A
PA (ICIL) IMPERIAL CHEM IND LTD
CYC 12
PI EP 20048 A 19801209 (198051)* EN
R: AT BE CH DE FR GB IT LI LU NL SE
JP 55157326 A 19801207 (198107)
PRAI GB 1979-18320 19790525
AB EP 20048 A UPAB: 19930902
Catalysts of Cu dispersed in silica are made by pptn. of a particulate solid Cu cpd. with silica from a mixt. of aq. Cu salt and **silicate** solns., then reducing to metallic Cu. The new feature is that the final pH of the mixed aq. solns. is 4-8, and esp. 5-7 when pptn. occurs.
Pref. both aq. solns. are mixed in small portions with vigorous stirring, so that pH 5-7.5 is rapidly established. Pref. Na **silicate** is used and the Cu cpd. pptd. is reduced with H2, opt. after **drying** and powdering, at 100-500 degrees C, esp. at 180 degrees C using pure H2 or at 180-500 degrees C using H2-N2 mixts.
These catalysts are useful for hydrogenation of organic cpds., e.g.

sugars to **alcohols**, with selectivity for one enantiomorph (e.g. an excess of **mannitol** from fructose); removing acetylene from olefins; hydrogenating soyabean oil etc. They have superior heat-**stability**, e.g. no loss of activity at up to 250 degrees, with small Cu particle sizes of all <25 nm, and mean particle size <10 nm.

L17 ANSWER 22 OF 24 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 1979-52596B [29] WPIDS
TI Stable solid compsns. contg. Gefarnate - having a carrier in which the surface is adjusted to pKa below 9.3.
DC B05
PA (ISTA) IST DE ANGELI SPA; (SUMO) SUMITOMO CHEM CO LTD
CYC 10
PI BE 874795 A 19790702 (197929)*
GB 2016271 A 19790926 (197939)
NL 7901917 A 19790918 (197940)
JP 54122718 A 19790922 (197944)
PT 69341 A 19791115 (197949)
FR 2419729 A 19791116 (198001)
ZA 7901103 A 19800211 (198015)
CS 7901652 A 19800915 (198101)
GB 2016271 B 19820902 (198235)
CH 637827 A 19830831 (198338)
JP 60026093 B 19850621 (198529)
IT 1162282 B 19870325 (198923)
PRAI JP 1978-29746 19780314
AB BE 874795 A UPAB: 19930901
Solid compositions contain Gefarnate as active ingredient, and a solid base as carrier, the surface of the carrier having been adjusted previously to a pKa of 9.3 or less by means of "adjusting agent" which is not a mono- or disaccharide, nor a **sugar alcohol**.

The solid carrier may be, for example, magnesium **silicate**, metamagnesium aluminosilicate, magnesium oxide, **dried** aluminium hydroxide gel, or synthetic hydrotalcite. The ''adjusting agent'' may be any mineral or organic acid, neutral, or weakly basic material, such as citric acid, or a natural or synthetic high polymer, especially polyvinyl alcohol or gum arabic. The adjustment of surface pKa is usually effected by dissolving the adjusting agent in a suitable solvent, adding the solid base, and **drying** the mixture. Alternatively the base and adjusting agent may be mixed, the solvent added, and the whole **dried**.

The compsns. are more stable than other solid Gefarnate compsns.

L17 ANSWER 23 OF 24 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 1978-04390A [03] WPIDS
TI Sand mould and core binder contg. **silicate** - and non-reducing polyol release agent having at least two alcoholic hydroxyl gps..
DC A81 M22 P53
PA (ROQF) ROQUETTE FRERES SA
CYC 2
PI DE 2629667 A 19780112 (197803)*
FR 2348771 A 19771223 (197806)
PRAI FR 1976-11650 19760421
AB DE 2629667 A UPAB: 19930901
Binder for sand casting-moulds and -cores consists of a mixt. of **silicate** and >=1 release agent for facilitating the release of blanks by removing the moulds and cores. Release agents consists, at least in part, of >1 non-reducing polyol, i.e. an organic cpd. other than a **sugar**, contg. >2 **alcoholic** OH gps. in its molecule.

Silicate content can be reduced. **Drying** is retarded. **Silicates** having a high modulus may be used. Moulds and cores may be removed before cooling, enabling release of blank quickly after casting. Binders have improved storage **stability**. Castings have an improved surface.

L17 ANSWER 24 OF 24 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 1977-16769Y [10] WPIDS
TI Casting process using alkali **silicate** binders - having high silica content, and treatment with diluted carbon dioxide.
DC M22 P53
PA (KATO-I) KATO A
CYC 4
PI DE 2637196 A 19770303 (197710)*
JP 52124418 A 19771019 (197748)
US 4121942 A 19781024 (197844)
GB 1557241 A 19791205 (197949)
JP 52024122 A 19770223 (198111)
JP 56006816 B 19810213 (198111)
PRAI JP 1975-100766 19750820; JP 1976-42086 19760414; JP 1976-42765 19760415
AB DE 2637196 A UPAB: 19930901
Moulding process comprises first mixing >=1 of Na **silicate** of mole ratio (m.r.) 2.7-4.5, K **silicate** of m.r. 2.5-5.0; Li **silicate** of m.r. 2.0-5.5 or alkali metal-ammonium **silicate** of m.r. 2.1-9.1 (SiO_2:alkali oxide) to a refractory material as binder. The mixt. is then pressed into shape and gasses with diluted OC_2, the diluent being a gas inert towards alkali **silicate** used to provide <=20 vol. % CO_2 in the mixt.

To inhibit reaction between CO_2 and **silicate** >=1 alkali-**stabilised** colloidal silica or a quat. ammonium **silicate**, or opt. 0.1-30 wt.% (an alkali **silicate**) of a (poly)saccharide or polyhydroxy **alcohol**, e.g. glucose, invert **sugar**, sucrose, sorbitol, **mannitol**, can be added.

CO_2 consumption is reduced to 1/2-1/20 of its normal value.

The articles are easily removed from the moulds. No undesirable gases are evolved during **drying** or casting. Contamination of the soil and water is avoided (contrast use of lower m.r. **silicates** which are more highly alkaline) and the sand can be reused.

search of claim 15

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=> d his

     (FILE 'HCAPLUS' ENTERED AT 11:44:22 ON 11 MAR 2002)
               DEL HIS Y

     FILE 'REGISTRY' ENTERED AT 11:44:39 ON 11 MAR 2002
               E MANNITOL/CN
L1             2 S E3
               E INOSITOL/CN
L2             2 S E3
               E XYLITOL/CN
               E ARABINITOL/CN
L3             1 S E3
               E GALACTITOL/CN
L4             1 S E3
               E DEXTRAN/CN
L5             1 S E3
               E CALCIUM LACTATE/CN
L6             1 S E3
               E PVP/CN
L7             1 S E3
               E BYCO C/CN
               E KOLLIDON 30/CN
L8             1 S E3

     FILE 'HCAPLUS' ENTERED AT 11:46:51 ON 11 MAR 2002
L9         13181 S MANNITOL OR L1
L10          824 S L9 AND (INOSITOL OR L2)
L11          546 S L9 AND (ARABINITOL OR L3)
L12          395 S L9 AND (DEXTRAN OR L5)
L13           30 S L10 AND L7

     FILE 'REGISTRY' ENTERED AT 11:49:32 ON 11 MAR 2002
               E XYLITOL/CN
L14            1 S E3

     FILE 'HCAPLUS' ENTERED AT 11:49:54 ON 11 MAR 2002
L15            2 S L10 AND (L14 OR XYLITOL) AND (L6 OR CALCIUM LACTATE)
L16            6 S L10 AND (L6 OR CALCIUM LACTATE)

     FILE 'REGISTRY' ENTERED AT 11:51:16 ON 11 MAR 2002
               E BYCO C/CN
L17            1 S E3

     FILE 'HCAPLUS' ENTERED AT 11:51:23 ON 11 MAR 2002
L18           92 S HID
L19            0 S L10 AND (L17 OR BYCO C)
L20            3 S L10 AND (CALCIUM LACTATE OR L6 ) AND (PVP OR L7)
L21            1 S L11 AND (L6 OR CALCIUM LACTATE)
L22            0 S L11 AND (L4 OR GALACTITOL ) AND (BYCO C OR L17)
L23            1 S L10 AND (L4 OR GALACTITOL ) AND (L6 OR CALCIUM LACTATE)
L24            0 S L9 AND (BYCO C OR L17) AND (L6 OR CALCIUM LACTATE)
               E L9 AND (L8 OR KOLLIDON 30)
L25          520 S L9 AND (L8 OR KOLLIDON 30)
L26            2 S L15 AND (L6 OR CALCIUM LACTATE)
L27          395 S L9 AND (L5 OR DEXTRAN)
L28            3 S L27 AND (L6 OR CALCIUM LACTATE)
L29          840 S L13 OR L15 OR L16  OR L19 OR L20 OR L21 OR L22 OR L23 OR L24
L30       452177 S GLASS? OR SILICAT?
L31           53 S L29 AND L30
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L32           6 S L31 AND (STABILIZ? OR AMORPHOUS?)
L33          19 S L31 AND (DRY? OR DRIED)
L34           6 S L33 AND (STABILI?/AB OR FACILITA? OR FACILITA?/AB)
L35          10 S L34 OR L32

=> d .ca hitstr 1-10

L35  ANSWER 1 OF 10  HCAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:        2001:792225  HCAPLUS
DOCUMENT NUMBER:         135:335183
TITLE:                   Stable glassy state powder formulations for
                         proteinaceous and other drugs
INVENTOR(S):             Foster, Linda C.; Kuo, Mei-chang; Billingsley, Shelia
                         R.
PATENT ASSIGNEE(S):      Inhale Therapeutic Systems, USA
SOURCE:                  U.S., 38 pp., Cont.-in-part of U.S. Ser. No. 733,225.
                         CODEN: USXXAM
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  7
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.   DATE
     ---------------   ----  --------      ---------------   --------
     US 6309671         B1   20011030      US 1997-950385    19971014
     US 6258341         B1   20010710      US 1996-733225    19961017
     AU 9923695         A1   19990708      AU 1999-23695     19990409
     AU 740760          B2   20011115
PRIORITY APPLN. INFO.:                  US 1995-423515    B2 19950414
                                        WO 1996-US5070    A2 19960412
                                        US 1996-733225    A2 19961017
                                        AU 1996-54827     A3 19960412
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AB A powd., dispersible compn. suitable for inhalation having stable dispersibility over time is provided. The compn. exhibits a characteristic glass transition temp. (Tg) and a recommended storage temp. (Ts), wherein the difference between Tg and Ts is at least about 10.degree. (i.e., Tg-Ts is greater than 10.degree.). The compn. comprises a mixt. of a pharmaceutically-acceptable glassy matrix and at least one pharmacol. active material within the glassy matrix. It may be further mixed with a powd., pharmaceutically-acceptable carrier. It is particularly valuable in unit dosage form having a moisture barrier, in combination with appropriate labeling instructions. A process for producing a powd. dispersible compn. is also provided, wherein the process comprises removing the solvent from a soln. comprising a solvent, a glass former and a pharmacol. active material under conditions sufficient to form a glassy matrix having the pharmacol. active material within the matrix. For example, a 60% insulin compn. that maintained protein integrity and aerosol **stability** after storage at 30.degree., 40.degree., 50.degree., and temp. cycling at 2-37.degree. was prepd. by spray drying of a soln. contg. 7.5 mg human zinc insulin, 1.27 mg mannitol, 3.38 mg sodium citrate, 0.026 mg sodium hydroxide, and 0.32 mg glycine per mL of water for a total solids concn. of 12.5 mg/mL at pH 7.3. The dry powder obtained contained 60.0% insulin, 2.6% glycine, 27.1% sodium citrate, 10.1% mannitol, and 0.2% sodium ion from sodium hydroxide. This formulation was remarkable in the fact that the powder could take up to 4.6% moisture without a loss of aerosol performance.

IC ICM A61K009-14
NCL 424489000
CC 63-6 (Pharmaceuticals)
ST protein drug **glassy** matrix powder inhalant

IT Humidity
(absorption; stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT Lung
(administration by; stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT Drug delivery systems
(aerosols, powders; stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT Containers
(moisture barrier-contg.; stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT Absorption
(moisture; stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT Drug delivery systems
(powders, inhalants; stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT Particle size
(prepn. of stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT Interleukin 1 receptors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(recombinant; stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT Carboxylic acids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(salts; stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT Albumins, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serum; stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT Evaporation
Precipitation (chemical)
(solvent removal by; prepn. of stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT **Drying**
(spray, solvent removal by; prepn. of stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT Storage
(stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT Amino acids, biological studies
Carbohydrates, biological studies
Caseins, biological studies
Peptides, biological studies
Polymers, biological studies
Polysaccharides, biological studies
Proteins, general, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)
IT **Glass** transition temperature
(stable **glassy** state powders with characteristic **glass** transition temp. suitable for inhalation)
IT **69-65-8**, D-**Mannitol** 77-86-1, Tromethamine 77-92-9, Citric acid, biological studies 1185-53-1, Tromethamine hydrochloride 9000-69-5, Pectin **9003-39-8**, Povidone
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

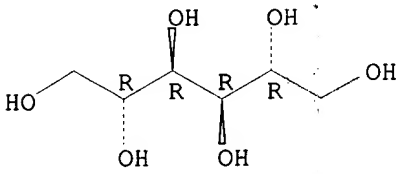
(stable **glassy** state powders suitable for inhalation for proteinaceous and other drugs)

IT 57-50-1, Sucrose, biological studies 63-42-3, Lactose 69-79-4, Maltose 99-20-7, Trehalose 470-55-3, Stachyose 512-69-6, Raffinose 528-50-7, Cellobiose 994-36-5, Sodium citrate 1109-28-0, Maltotriose 3632-91-5, Magnesium gluconate 8049-62-5, Zinc insulin 9004-10-8, Insulin, biological studies 9005-27-0, Hydroxyethyl starch 9041-92-3, .alpha.1-Antitrypsin 9050-36-6, Maltodextrin 12619-70-4, Cyclodextrin 18559-94-9, Albuterol 47931-85-1, Salmon calcitonin 51022-70-9, Albuterol sulfate 60731-46-6, Elcatonin 63213-92-3 68424-04-4, Polydextrose 134613-11-9
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stable **glassy** state powders suitable for inhalation of proteinaceous and other drugs)

IT **69-65-8**, D-**Mannitol 9003-39-8**, Povidone
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stable **glassy** state powders suitable for inhalation for proteinaceous and other drugs)

RN 69-65-8 HCAPLUS
CN D-Mannitol (9CI) (CA INDEX NAME)

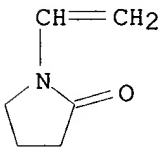
Absolute stereochemistry.



RN 9003-39-8 HCAPLUS
CN 2-Pyrrolidinone, 1-ethenyl-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 88-12-0
CMF C6 H9 N O



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 2 OF 10 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:416803 HCAPLUS
DOCUMENT NUMBER: 135:24708
TITLE: A rapid acting freeze-**dried** oral pharmaceutical composition for treating migraine
INVENTOR(S): Venkateswara Rao, Pavuluri; Khadgapathi, Podili
PATENT ASSIGNEE(S): Natco Pharma Limited, India
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001039836	A1	20010607	WO 2000-IN78	20000825

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: IN 1999-MA1160 A 19991201

AB The present invention relates to a novel rapid-acting freeze-dried pharmaceutical compn. useful for the treatment of migraine and assocd. symptoms at a reduced total dose of active substance than required for oral administration in the form of a tablet. The compn. contains a porous matrix network of a water sol. or water dispersible carrier material, a pharmaceutically active substance(s), organoleptic additives such as sweetening agents, flavoring agents, and coloring agents, pharmaceutically acceptable preservatives, solubilizing agents, surface active agents and/or buffering agents. The pharmaceutical compn. optionally may contain other additives such as permeation enhancers, chelating salts and **stabilizing** agents. Advantages of the invention are: (1) rapid onset of action due to the rapid absorption of the active substance through oral mucosa, (2) reduced dosage of the drugs as absorption through oral mucosa bypasses the first-pass metab. and overcomes possible degrdn. in the gastrointestinal tract, (3) easy to administer to pediatric and geriatric patients, and (4) medicament can be taken without water. For example, tablets were prepd. by freeze drying to contain sumatriptan succinate 14.00 mg, ondansetron hydrochloride 5.0 mg, citric acid 1.68 mg, Na2HPO4 2.42 mg, polyvinyl chloride 3.0%, mannitol 25%, Me paraben sodium 0.1%, and Pr paraben sodium 0.01%.

IC ICM A61P025-06
ICS A61K031-48; A61K031-42; A61K031-4196; A61K031-4045; A61K031-138; A61K009-19

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1

ST antimigraine oral pharmaceutical freeze **drying**

IT Preservatives
(antimicrobial; rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)

IT Vinyl compounds, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carboxy-contg., polymers; rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)

IT Gelatins, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydrolyzates; rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)

IT Mouth
(mucosa, absorption by; rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)

IT Drug delivery systems
(oral; rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)

IT Antimicrobial agents
(preservatives; rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)
IT Adrenoceptor agonists
Allergy inhibitors
Analgesics
Anti-inflammatory agents
Antiemetics
Antihistamines
Antimigraine agents
Buffers
Coloring materials
Flavoring materials
Freeze **drying**
Solubilizers
Stabilizing agents
Surfactants
Sweetening agents
(rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)
IT Bile salts
Carbohydrates, biological studies
Gelatins, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)
IT Fatty acids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(salts; rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)
IT Drug delivery systems
(tablets; rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)
IT Fatty acids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(unsatd., salts; rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)
IT 113-15-5, Ergotamine 379-79-3, Ergotamine tartrate 525-66-6, Propranolol 99614-01-4, Ondansetron hydrochloride 103628-46-2, Sumatriptan 103628-48-4, Sumatriptan succinate 139264-17-8, Zolmitriptan
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)
IT 58-38-8, Prochlorperazine 58-73-1, Diphenhydramine 90-82-4, Pseudoephedrine 103-90-2, Paracetamol 113-92-8, Chlorpheniramine maleate 364-62-5, Metoclopramide 523-87-5, Dimenhydrinate **9003-39-8**, Polyvinylpyrrolidone 14838-15-4, Phenylpropanolamine 26159-34-2, Naproxen sodium 50679-08-8, Terfenadine 52468-60-7, Flunarizine 57808-66-9, Domperidone 83881-51-0, Cetirizine 99614-02-5, Ondansetron 109889-09-0, Granisetron
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)
IT 50-99-7, Dextrose, biological studies 59-23-4, Galactose, biological studies 60-00-4D, Edetic acid, salts 63-42-3, Lactose **69-65-8**, D-**Mannitol** 77-92-9, Citric acid, biological studies 77-92-9D, Citric acid, salts 151-21-3, Sodium lauryl sulfate, biological

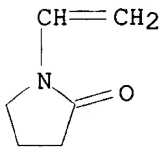
studies 302-95-4, Sodium deoxycholate 361-09-1, Sodium cholate 516-50-7, Taurodeoxycholic acid 577-11-7, Docusate sodium 863-57-0, Sodium glycocholate 994-36-5, Sodium citrate 1335-30-4, Aluminum **silicate** 5026-62-0, Methylparaben sodium 7558-79-4 7632-05-5, Sodium phosphate 7647-14-5, Sodium chloride, biological studies 9000-69-5, Pectin 9002-89-5, Polyvinylalcohol 9004-32-4, Carboxymethyl cellulose 9004-53-9, Dextrin 9004-62-0, Hydroxyethyl cellulose 9004-64-2, Hydroxypropyl cellulose 9004-67-5, Methyl cellulose 9005-32-7, Alginic acid 12441-09-7D, Sorbitan, esters 12619-70-4, Cyclodextrin 16409-34-0, Sodium glycodeoxycholate 35285-69-9, Propylparaben sodium 57916-92-4, carbomer 934P 151687-96-6, carbomer 974P
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)

IT **9003-39-8**, Polyvinylpyrrolidone
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)

RN 9003-39-8 HCAPLUS
CN 2-Pyrrolidinone, 1-ethenyl-, homopolymer (9CI) (CA INDEX NAME)

CM 1

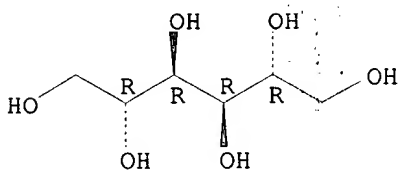
CRN 88-12-0
CMF C6 H9 N O



IT **69-65-8**, D-**Mannitol**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rapid-acting freeze-**dried** oral pharmaceuticals for migraine treatment)

RN 69-65-8 HCAPLUS
CN D-Mannitol (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 3 OF 10 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:129878 HCAPLUS
DOCUMENT NUMBER: 134:183489
TITLE: Composition for stable injectable liquids containing

perfluorocarbons

INVENTOR(S): Roser, Bruce Joseph; Garcia De Castro, Arcadio; Maki, James

PATENT ASSIGNEE(S): Peter M. Ronai, USA

SOURCE: U.S., 9 pp.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6190701	B1	20010220	US 1999-271204	19990317

AB A compn. for delivering a stable, bioactive compd. to a subject comprising a first component and a second component, the first component comprises microparticles of sugar glass or a phosphate glass contg. the bioactive agent. The sugar glass or phosphate glass optionally includes a glass formation facilitator compd. The second component comprises at least one biocompatible liq. perfluorocarbon in which the first component is insol. and dispersed. The liq. perfluorocarbon optionally includes a surfactant. For example, alk. phosphatase was stabilized in a glass based on mannitol 33.3%, calcium phosphate 33.3% and degraded gelatin 33.3 %, spray dried as microspheres and stored at 55.degree. either as the dry powder or as a suspension in perfluorodecalin. The enzyme microspheres suspended in perfluorodecalin show retention of close to 100% of enzyme activity for > 30 days at 55.degree..

IC ICM A61K009-50
ICS B32B015-16

NCL 424499000

CC 63-6 (Pharmaceuticals)

ST drug enzyme vaccine **stabilization glass** microparticle; perfluorocarbon phosphate sugar **glass** microparticle injection

IT Diagnosis
(agents; injectable compns. contg. drugs, enzymes, and vaccines **stabilized** in sugar or phosphate **glasses** and liq. perfluorocarbons)

IT Gelatins, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(degraded; injectable compns. contg. drugs, enzymes, and vaccines **stabilized** in sugar or phosphate **glasses** and liq. perfluorocarbons)

IT Phosphates, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(divalent metal, **glasses**; injectable compns. contg. drugs, enzymes, and vaccines **stabilized** in sugar or phosphate **glasses** and liq. perfluorocarbons)

IT Carbohydrates, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**glasses**; injectable compns. contg. drugs, enzymes, and vaccines **stabilized** in sugar or phosphate **glasses** and liq. perfluorocarbons)

IT Electrostatic charge
Particle size
Stabilizing agents
Surfactants
Vaccines
(injectable compns. contg. drugs, enzymes, and vaccines **stabilized** in sugar or phosphate **glasses** and liq. perfluorocarbons)

IT Enzymes, biological studies
RL: PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(injectable compns. contg. drugs, enzymes, and vaccines **stabilized** in sugar or phosphate **glasses** and liq. perfluorocarbons)

IT Alditols
Amino acids, biological studies
Peptides, biological studies
Perfluorocarbons
Phosphate **glasses**
Proteins, general, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(injectable compns. contg. drugs, enzymes, and vaccines **stabilized** in sugar or phosphate **glasses** and liq. perfluorocarbons)

IT Drug delivery systems
(injections; injectable compns. contg. drugs, enzymes, and vaccines **stabilized** in sugar or phosphate **glasses** and liq. perfluorocarbons)

IT Carboxylic acids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(metal salts, **glasses**; injectable compns. contg. drugs, enzymes, and vaccines **stabilized** in sugar or phosphate **glasses** and liq. perfluorocarbons)

IT Drug delivery systems
(microparticles; injectable compns. contg. drugs, enzymes, and vaccines **stabilized** in sugar or phosphate **glasses** and liq. perfluorocarbons)

IT Drug delivery systems
(microspheres; injectable compns. contg. drugs, enzymes, and vaccines **stabilized** in sugar or phosphate **glasses** and liq. perfluorocarbons)

IT Polyphosphoric acids
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sodium salts; injectable compns. contg. drugs, enzymes, and vaccines **stabilized** in sugar or phosphate **glasses** and liq. perfluorocarbons)

IT 9001-78-9, Alkaline phosphatase
RL: PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(injectable compns. contg. drugs, enzymes, and vaccines **stabilized** in sugar or phosphate **glasses** and liq. perfluorocarbons)

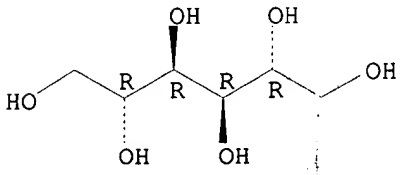
IT 56-40-6, Glycine, biological studies 56-87-1, Lysine, biological studies 57-50-1, Sucrose, biological studies **69-65-8, Mannitol** **87-89-8, Inositol** 99-20-7, Trehalose 126-14-7, Sucrose octaacetate 127-09-3, Sodium acetate 306-94-5, Perfluorodecalin 330-13-2, p-Nitrophenyl phosphate 355-42-0, Perfluorohexane 470-55-3, Stachyose 512-69-6, Raffinose 585-86-4, Lactitol **814-80-2, Calcium lactate** 1344-09-8, Sodium **silicate** 1580-20-7, Perfluorophenanthrene 7646-85-7, Zinc chloride, biological studies 7757-82-6, Sodium sulfate, biological studies 7786-30-3, Magnesium chloride, biological studies **9003-39-8 9004-54-0, Dextran**, biological studies 10103-46-5, Calcium phosphate 14213-97-9, Borate 21645-51-2, Aluminum hydroxide, biological studies 25018-27-3, Trehalose octaacetate 63213-92-3 64519-82-0, Palatinit 134613-11-9
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(injectable compns. contg. drugs, enzymes, and vaccines

stabilized in sugar or phosphate **glasses** and liq. perfluorocarbons)

IT **69-65-8, Mannitol 87-89-8, Inositol 814-80-2, Calcium lactate 9003-39-8 9004-54-0, Dextran,** biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(injectable compns. contg. drugs, enzymes, and vaccines **stabilized** in sugar or phosphate **glasses** and liq. perfluorocarbons)

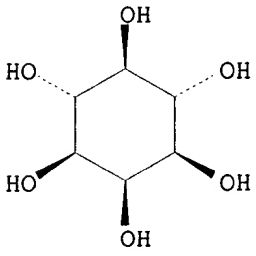
RN 69-65-8 HCAPLUS
CN D-Mannitol (9CI) (CA INDEX NAME)

Absolute stereochemistry.

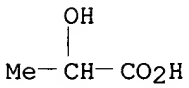


RN 87-89-8 HCAPLUS
CN myo-Inositol (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 814-80-2 HCAPLUS
CN Propanoic acid, 2-hydroxy-, calcium salt (2:1) (9CI) (CA INDEX NAME)

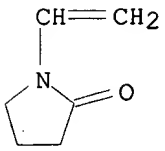


1/2 Ca

RN 9003-39-8 HCAPLUS
CN 2-Pyrrolidinone, 1-ethenyl-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 88-12-0
CMF C6 H9 N O



RN 9004-54-0 HCAPLUS
CN Dextran (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 4 OF 10 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:462502 HCAPLUS
DOCUMENT NUMBER: 133:40215
TITLE: Bi-mediator-based multi-enzyme biosensor and its application
INVENTOR(S): Guo, Dingli; Shieh, Paul; Goldberg, Esfir
PATENT ASSIGNEE(S): Biomedix Inc., USA, USA
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 32 pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

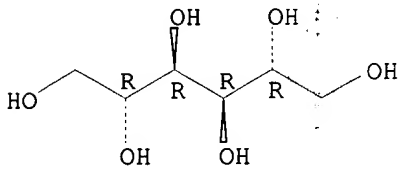
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1219676	A	19990616	CN 1998-123464	19981027
US 6033866	A	20000307	US 1997-986974	19971208

PRIORITY APPLN. INFO.: US 1997-986974 A 19971208

AB The biosensor consists of sensitive electrode with the first redox mediator, reagent carrying strip made of porous fiber, and ref. electrode. The biosensor may have red blood cell filtering membrane set between the reagent carrying strip and the ref. electrode. The reagent carrying strip contains enzymes, the second redox mediator, surfactant, stabilizing agent, and pH buffering agent. The reagent carrying strip is set between the sensitive electrode and the ref. electrode, or is set on the conducting layers of the electrodes. The first redox mediator is from ferrocene ion or carboxylic acid ferrocene, benzoquinone, tetrathiofulvalene, ferrocene, dimethylferrocene, hydroquinone. The second redox mediator is from tetramethylbenzidine, o-dianisidine, o-toluidine, and aminophenazone, aminoantipyrine and aminoantipyrine and dimethylaniline, CN-, Fe(CN)64-, Co(NH3)62+, Sn2+, S2-, etc. The surfactant is from Triton X-100, Na lauryl sulfate, lauryl sarcosine Na salt, hydroxypropylmethylcellulose, capryl amphoteric carboxylpropionate. The stabilizing agent is from animal glue, agar, bovine serum albumin, glutamine, mannitol, arabic gum, and polypeptide methylcellulose. The pH buffering agent is from citrate, succinate, trihydroxymethylaminomethane, phosphate. The red blood cell filtering membrane is from polysulfone film, polysulfone or polycarbonate film with polyvinylpyrrolidone, poly(vinyl alc.), poly(acrylic acid), animal glue, ethylcellulose, or glass fiber film with polyvinylpyrrolidone, poly(vinyl alc.), poly(acrylic acid), alginic acid, animal glue, ethylcellulose, or polyvinyl glycol stearate. The anal. method using the biosensor comprises putting blood onto the sampling site of the ref. electrode, exerting static voltage between the ref. electrode and the sensitive electrode, detg. the current flow through the electrodes, establishing calibration curve of blood

substrate concn. vs. the current, and detg. the substrate concn. of blood sample.
IC ICM G01N027-00
CC 9-1 (Biochemical Methods)
IT Blood
Blood analysis
Buffers
Calibration
Electric conductivity
Electric current
Electric potential
Electrodes
Erythrocyte
Films
Glues
Membrane filters
Reference electrodes
Sampling
Stabilizing agents
Surfactants
(Bi-mediator-based multi-enzyme biosensor and application)
IT **Glass** fibers, uses
Polycarbonates, uses
Polysulfones, uses
RL: DEV (Device component use); USES (Uses)
(Bi-mediator-based multi-enzyme biosensor and application)
IT 56-85-9, Glutamine, uses **69-65-8**, D-**Mannitol**
77-92-9, uses 110-15-6, Butanedioic acid, uses 151-21-3, Sodium lauryl sulfate, uses 7631-98-3, Lauryl sarcosine sodium salt 9000-01-5, Arabic gum 9002-18-0, Agar 9002-89-5, Poly(vinyl alcohol) 9002-93-1, Triton X-100 9003-01-4, Poly(acrylic acid) **9003-39-8**, Polyvinylpyrrolidone 9004-57-3, Ethylcellulose 9004-65-3, Hydroxypropylmethylcellulose 9005-32-7, Alginic acid 14265-44-2, Phosphate, uses
RL: DEV (Device component use); USES (Uses)
(Bi-mediator-based multi-enzyme biosensor and application)
IT **69-65-8**, D-**Mannitol** **9003-39-8**,
Polyvinylpyrrolidone
RL: DEV (Device component use); USES (Uses)
(Bi-mediator-based multi-enzyme biosensor and application)
RN 69-65-8 HCAPLUS
CN D-Mannitol (9CI) (CA INDEX NAME)

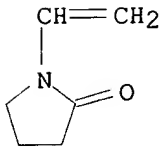
Absolute stereochemistry.



RN 9003-39-8 HCAPLUS
CN 2-Pyrrolidinone, 1-ethenyl-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 88-12-0
CMF C6 H9 N O



L35 ANSWER 5 OF 10 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:401969 HCAPLUS
DOCUMENT NUMBER: 133:28260
TITLE: Method and composition for preserving viruses
INVENTOR(S): Kovesdi, Imre; Ransom, Stephen C.
PATENT ASSIGNEE(S): Genvec, Inc., USA
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000034444	A2	20000615	WO 1999-US29271	19991210
WO 2000034444	A3	20001026		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6225289	B1	20010501	US 1998-208666	19981210
EP 1137758	A2	20011004	EP 1999-966096	19991210
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2002019041	A1	20020214	US 2001-870920	20010531

PRIORITY APPLN. INFO.: US 1998-208666 A 19981210
WO 1999-US29271 W 19991210

AB The present invention provides a method and a compn. for preserving a virus. The virus is placed in a liq. carrier with a stabilizing agent selected from the group consisting of polysorbate 80, L-arginine, polyvinylpyrrolidone, trehalose, and combinations thereof. The liq. compn. can be maintained at a temp. above 0 .degree.C for a significant period of time while maintaining a satisfactory degree of viral activity.

IC ICM C12N007-00
CC 9-11 (Biochemical Methods)
Section cross-reference(s): 10, 63
ST virus preservation **stabilizing** agent
IT **Glass**, uses
Plastics, uses
RL: DEV (Device component use); USES (Uses)
(container; method and compn. for preserving viruses)
IT Drug delivery systems
Preservation
Preservatives

Stabilizing agents
Virus
(method and compn. for preserving viruses)

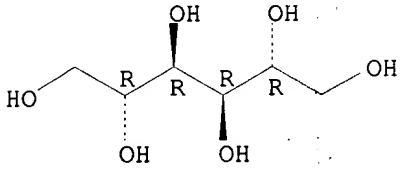
IT 50-70-4, Sorbitol, biological studies 50-99-7, Dextrose, biological studies 57-50-1, Sucrose, biological studies **69-65-8, Mannitol**
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(as **stabilizing** agent; method and compn. for preserving viruses)

IT 74-79-3, L-Arginine, biological studies 99-20-7, Trehalose **9003-39-8**, Polyvinylpyrrolidone 9005-65-6, Polysorbate 80
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(method and compn. for preserving viruses)

IT **69-65-8, Mannitol**
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(as **stabilizing** agent; method and compn. for preserving viruses)

RN 69-65-8 HCAPLUS
CN D-Mannitol (9CI) (CA INDEX NAME)

Absolute stereochemistry.

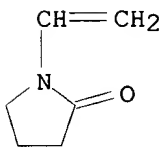


IT **9003-39-8**, Polyvinylpyrrolidone
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(method and compn. for preserving viruses)

RN 9003-39-8 HCAPLUS
CN 2-Pyrrolidinone, 1-ethenyl-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 88-12-0
CMF C6 H9 N O



L35 ANSWER 6 OF 10 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:613714 HCAPLUS
DOCUMENT NUMBER: 131:248244
TITLE: **Amorphous glasses** for **stabilizing** sensitive products
INVENTOR(S): Roser, Bruce Joseph; De Castro, Arcadio Garcia

PATENT ASSIGNEE(S): Cambridge Biostability Limited, UK
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9947174	A1	19990923	WO 1999-GB820	19990317
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9929451	A1	19991011	AU 1999-29451	19990317
EP 1071465	A1	20010131	EP 1999-910516	19990317
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: GB 1998-5699 A 19980318
GB 1998-20689 A 19980923
WO 1999-GB820 W 19990317

AB A method of drying, without damage, a compd. which is subject to deactivation on drying, or a mixt. of such compds., comprises subjecting an aq. system contg. the compd. or mixt. to drying in the presence of .gtoreq.1 chem. inert monosaccharide sugar alc. and .gtoreq.1 additive which is a glass-former or a glass formation **facilitator**, whereby the compd. solidifies from soln. as an amorphous glass rather than by forming crystals. This method is useful for drying compds. at or above room temp. which are otherwise subject to deactivation on drying. Thus, alk. phosphatase, vacuum-dried or freeze-dried in a glass-forming blend of mannitol 30, inositol 15, galactitol 15, and Byco C (degraded gelatin) 40%, was stable during storage at 37.degree. or 50.degree. for 5 wk.

IC ICM A61K047-26
ICS A61K047-22; A23L001-275; A61K007-00; A61K009-00
CC 63-6 (Pharmaceuticals)
ST sugar alc **glass stabilizer** protein; heat **stabilizer** protein hexitol **glass**

IT Phycoerythrins
RL: PEP (Physical, engineering or chemical process); PROC (Process)
(R-phycoerythrins; **amorphous glasses** for **stabilizing** sensitive products)

IT Denaturation
Drying
Freeze **drying**
Stabilizing agents
(**amorphous glasses** for **stabilizing** sensitive products)

IT **Glass**, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**amorphous glasses** for **stabilizing** sensitive products)

IT Gelatins, biological studies
Peptides, biological studies
Phosphates, biological studies

Silicates, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**glasses** contg.; **amorphous glasses** for **stabilizing** sensitive products)

IT Alditols
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**glasses**; **amorphous glasses** for **stabilizing** sensitive products)

IT Crystallization
(inhibitors; **amorphous glasses** for **stabilizing** sensitive products)

IT Fluorescent substances
(proteins, **stabilization** of; **amorphous glasses** for **stabilizing** sensitive products)

IT Albumins, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serum, crystn. inhibitors; **amorphous glasses** for **stabilizing** sensitive products)

IT **Drying**
(spray; **amorphous glasses** for **stabilizing** sensitive products)

IT Blood serum
Vaccines
(**stabilization** of; **amorphous glasses** for **stabilizing** sensitive products)

IT Antibodies
Antigens
Complement
Enzymes, biological studies
Nucleic acids
Polysaccharides, biological studies
Proteins, general, biological studies
RL: BAC (Biological activity or effector, except adverse); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**stabilization** of; **amorphous glasses** for **stabilizing** sensitive products)

IT **Drying**
(vacuum; **amorphous glasses** for **stabilizing** sensitive products)

IT 9001-78-9 11096-26-7, Erythropoietin
RL: BAC (Biological activity or effector, except adverse); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**amorphous glasses** for **stabilizing** sensitive products)

IT 99-20-7, Trehalose 64519-82-0, Palatinit
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(crystn. inhibitor; **amorphous glasses** for **stabilizing** sensitive products)

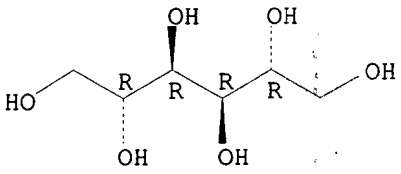
IT 64-19-7D, Acetic acid, salts **69-65-8**, D-**Mannitol** **87-89-8**, myo-**Inositol** **87-99-0**, **Xylitol** 488-81-3, Adonitol **608-66-2**, **Galactitol** **814-80-2**, **Calcium lactate** 1330-43-4D, Sodium tetraborate, salts 1332-77-0D, Potassium tetraborate, salts **2152-56-9**, **Arabinitol** **9003-39-8D**, **PVP**, salts **9004-54-0**, **Dextran**, biological studies 10043-35-3D, Boric acid, salts 11129-12-7, Borate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**glasses** contg.; **amorphous glasses** for

stabilizing sensitive products)

IT **69-65-8**, D-**Mannitol 87-89-8**, myo-**Inositol 87-99-0**, **Xylitol 608-66-2**, **Galactitol 814-80-2**, **Calcium lactate 2152-56-9**, **Arabinitol 9003-39-8D**, **PVP**, salts **9004-54-0**, **Dextran**, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**glasses** contg.; **amorphous glasses** for **stabilizing** sensitive products)

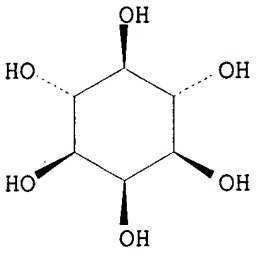
RN 69-65-8 HCAPLUS
CN D-Mannitol (9CI) (CA INDEX NAME)

Absolute stereochemistry.

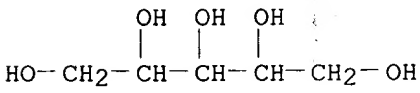


RN 87-89-8 HCAPLUS
CN myo-Inositol (9CI) (CA INDEX NAME)

Relative stereochemistry.

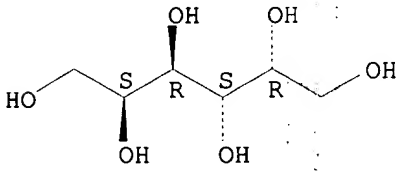


RN 87-99-0 HCAPLUS
CN Xylitol (6CI, 8CI, 9CI) (CA INDEX NAME)

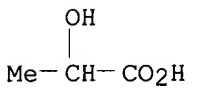


RN 608-66-2 HCAPLUS
CN Galactitol (6CI, 8CI, 9CI) (CA INDEX NAME)

Relative stereochemistry.

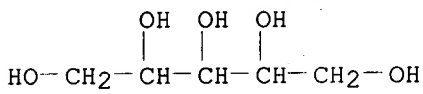


RN 814-80-2 HCAPLUS
CN Propanoic acid, 2-hydroxy-, calcium salt (2:1) (9CI) (CA INDEX NAME)



●1/2 Ca

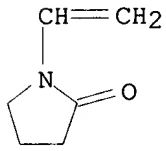
RN 2152-56-9 HCAPLUS
CN Arabinitol (8CI, 9CI) (CA INDEX NAME)



RN 9003-39-8 HCAPLUS
CN 2-Pyrrolidinone, 1-ethenyl-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 88-12-0
CMF C6 H9 N O



RN 9004-54-0 HCAPLUS
CN Dextran (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 7 OF 10 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:31050 HCAPLUS
DOCUMENT NUMBER: 130:227652
TITLE: Effects of Additives on the Stability of Humicola lanuginosa Lipase during Freeze-**Drying** and Storage in the **Dried** Solid
AUTHOR(S): Kreilgaard, Lotte; Frokjaer, Sven; Flink, James M.; Randolph, Theodore W.; Carpenter, John F.
CORPORATE SOURCE: Department of Pharmaceutical Sciences School of Pharmacy, University of Colorado Health Sciences Center, Denver, CO, 80262, USA
SOURCE: J. Pharm. Sci. (1999), 88(3), 281-290
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The effects of various classes of additives on the **stability** of a protein with a relatively hydrophobic surface, Humicola lanuginosa lipase (HLL), during lyophilization and storage in the dried solid, were investigated. Prior to lyophilization, it was found that 1M trehalose or 1% Tween 20 caused the protein to ppt. IR spectroscopy indicated that trehalose "salted-out" native HLL, whereas Tween 20 induced non-native aggregates. Optimal recovery of native protein in the initial dried solid was obtained in the presence of additives which formed an amorphous phase and which had the capacity to hydrogen bond to the dried protein (e.g., trehalose and sucrose). Additives which crystd. during lyophilization (e.g., mannitol) or which remained amorphous, but were unable to hydrogen bond to the dried protein (e.g., dextran), afforded less **stabilization** relative to that seen in the absence of additives. Optimal storage **stability** in the dried solid required that both protein unfolding during lyophilization was minimized and that the formulation was stored at a temp. below its Tg value. Crystn. of sucrose during storage greatly reduced the storage **stability** of HLL. This was attributed to the increased moisture content and the reduced Tg value in the remaining amorphous phase contg. the protein. Sucrose crystn. and the resulting damage to the protein were inhibited by decreasing the mass ratio of sucrose:protein.

CC 63-5 (Pharmaceuticals)

ST additive stability lipase freeze **drying** storage

IT Crystallization
Freeze **drying**
Glass transition temperature
(additives effect on stability of lipase during freeze-**drying** and storage in **dried** solid)

IT Proteins (general), biological studies
RL: PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(additives effect on stability of lipase during freeze-**drying** and storage in **dried** solid)

IT 9001-62-1, Lipase
RL: PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(Humicola lanuginosa; additives effect on stability of lipase during freeze-**drying** and storage in **dried** solid)

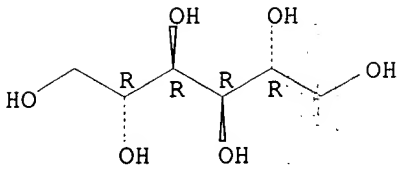
IT 57-50-1, Sucrose, biological studies **69-65-8**, D-**Mannitol**
99-20-7, Trehalose **9004-54-0**, **Dextran**, biological studies 9005-64-5, Tween 20
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(additives effect on stability of lipase during freeze-**drying** and storage in **dried** solid)

IT **69-65-8**, D-**Mannitol** **9004-54-0**, **Dextran**
, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(additives effect on stability of lipase during freeze-**drying** and storage in **dried** solid)

RN 69-65-8 HCAPLUS

CN D-Mannitol (9CI) (CA INDEX NAME)

Absolute stereochemistry.



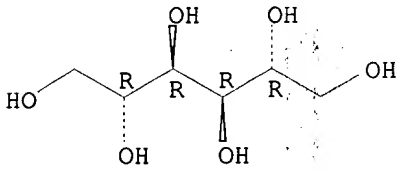
RN 9004-54-0 HCAPLUS
CN Dextran (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 8 OF 10 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:797798 HCAPLUS
DOCUMENT NUMBER: 130:129859
TITLE: Effects of additives on the stability of recombinant human factor XIII during freeze-**drying** and storage in the **dried** solid
AUTHOR(S): Kreilgaard, Lotte; Frokjaer, Sven; Flink, James M.; Randolph, Theodore W.; Carpenter, John F.
CORPORATE SOURCE: Department of Pharmaceutics, The Royal Danish School of Pharmacy, Copenhagen, 80262, Den.
SOURCE: Arch. Biochem. Biophys. (1998), 360(1), 121-134
CODEN: ABBIA4; ISSN: 0003-9861
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Freeze-drying is often used to improve storage **stability** of therapeutic proteins. In order to obtain a product with optimal storage **stability** it is important to understand the mechanisms by which solutes protect the protein against freeze-drying-induced stresses and also against damage induced during subsequent storage. The objective of the current study was to examine the importance of various mechanisms proposed to account for acute and long-term storage **stability** using recombinant human Factor XIII (rFXIII) as a model protein. Initially, for acute **stability** during freeze-drying, it was found that solutes which formed an amorphous phase **stabilized** rFXIII to a greater degree than solutes which crystd. during freeze-drying. However, only amorphous solutes which were able to hydrogen bond to the protein, and thus preserve the native protein structure in the dried solid, provided optimal acute **stability**. Thus, in addn. to forming an amorphous phase, it was also important to possess the ability to hydrogen bond to the protein. Long-term storage **stability** was optimal in the presence of solutes which formed and maintained amorphous phases with Tg values above the storage temp. and which also preserved the native protein structure during freeze-drying. Solute crystn. during storage compromised storage **stability**.
(c) 1998 Academic Press.
CC 63-5 (Pharmaceuticals)
ST additive stability factor XIII freeze **drying**
IT Aggregation
Conformation
Freeze **drying**
Glass transition temperature
(additives effect on stability of recombinant human factor XIII during freeze-**drying** and storage in **dried** solid)

IT Polyoxyalkylenes, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(additives effect on stability of recombinant human factor XIII during freeze-**drying** and storage in **dried** solid)
IT 57-50-1, Sucrose, biological studies **69-65-8**, D-**Mannitol** 99-20-7, Trehalose **9004-54-0**, **Dextran**, biological studies 9005-64-5, Tween 20 25322-68-3, Polyethylene glycol
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(additives effect on stability of recombinant human factor XIII during freeze-**drying** and storage in **dried** solid)
IT 9013-56-3, Factor XIII
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(recombinant human; additives effect on stability of recombinant human factor XIII during freeze-**drying** and storage in **dried** solid)
IT **69-65-8**, D-**Mannitol** **9004-54-0**, **Dextran**, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(additives effect on stability of recombinant human factor XIII during freeze-**drying** and storage in **dried** solid)
RN 69-65-8 HCAPLUS
CN D-Mannitol (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 9004-54-0 HCAPLUS
CN Dextran (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 9 OF 10 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:210839 HCAPLUS
DOCUMENT NUMBER: 128:215275
TITLE: **Stabilizing** biological material in a collapsed matrix of a non-carbohydrate polymeric material
INVENTOR(S): Murray, Donna Christine; Rodham, David Kirk; D'Alwis, Bernard; Cantwell, John Burnett; Rhodes, David John; Bradley, Sandra Samira
PATENT ASSIGNEE(S): Zeneca Ltd., UK; Murray, Donna Christine; Rodham, David Kirk; D'Alwis, Bernard; Cantwell, John Burnett; Rhodes, David John; Bradley, Sandra Samira
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9813471	A1	19980402	WO 1997-GB2566	19970922
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9743127	A1	19980417	AU 1997-43127	19970922
EP 929660	A1	19990721	EP 1997-941102	19970922
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001501091	T2	20010130	JP 1998-515377	19970922
PRIORITY APPLN. INFO.:			GB 1996-19893 A	19960924
			WO 1997-GB2566 W	19970922

AB This invention describes a compn. comprising a stabilized biol. material in a stasis state suspended in a collapsed matrix of a non-carbohydrate polymeric material capable of forming a glassy state. The matrix is also characterized in that it incorporates urea. The matrix may also contain trimethylammonium oxide. The compn. may also consist of PVP, or other polymeric species, antioxidants, sugars and osmoregulants. This invention is particularly applicable to microbes such as bacteria, fungi and yeast. In particular, Pseudomonas fluorescens is discussed. The use of non-carbohydrate polymeric material is emphasized since carbohydrate polymers tend to stimulate the growth of pathogens and other organisms.

IC ICM C12N001-04
ICS C12N011-04; C12N011-08
CC 9-16 (Biochemical Methods)
Section cross-reference(s): 10
ST microorganism **stabilization** non carbohydrate polymer urea
IT Encapsulation
(agents; **stabilizing** biol. material in collapsed matrix of a non-carbohydrate polymeric material)
IT Immobilization (biological cell)
(microbial cell; **stabilizing** biol. material in collapsed matrix of a non-carbohydrate polymeric material)
IT Polymers, biological studies
RL: BUU (Biological use, unclassified); POF (Polymer in formulation); TEM (Technical or engineered material use); BIOL (Biological study); USES (Uses)
(non-carbohydrate; **stabilizing** biol. material in collapsed matrix of a non-carbohydrate polymeric material)
IT Soil bacteria
(rhizospheric; **stabilizing** biol. material in collapsed matrix of a non-carbohydrate polymeric material)
IT Antioxidants
Bacillus thuringiensis
Bacteria (Eubacteria)
Bradyrhizobium
Cell (biological)
Encapsulation
Escherichia coli
Fungi
Glass structure

Glass transition temperature
Immobilization (biological cell)
Immobilization (molecular)
Matrix media
Microorganism
Osmolytes
Preservation
Pseudomonas
Pseudomonas fluorescens
Pythium ultimum
Rhizobium
Stabilizing agents
Storage
Yeast
(**stabilizing** biol. material in collapsed matrix of a non-carbohydrate polymeric material)

IT Carbohydrates, biological studies
RL: BUU (Biological use, unclassified); MOA (Modifier or additive use); TEM (Technical or engineered material use); BIOL (Biological study); USES (Uses)
(**stabilizing** biol. material in collapsed matrix of a non-carbohydrate polymeric material)

IT Polyoxyalkylenes, biological studies
RL: BUU (Biological use, unclassified); POF (Polymer in formulation); TEM (Technical or engineered material use); BIOL (Biological study); USES (Uses)
(**stabilizing** biol. material in collapsed matrix of a non-carbohydrate polymeric material)

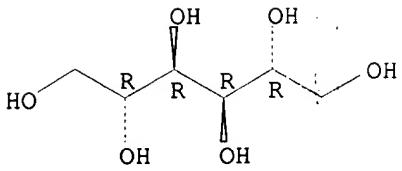
IT 50-81-7, Ascorbic acid, biological studies 50-99-7, Glucose, biological studies 56-12-2, GABA, biological studies 57-13-6, Urea, biological studies **69-65-8, Mannitol** 107-43-7, Betaine 107-97-1, Sarcosine 134-03-2, Sodium ascorbate 147-85-3, Proline, biological studies 1184-78-7 9050-36-6, Maltodextrin 16177-21-2, Sodium glutamate
RL: BUU (Biological use, unclassified); MOA (Modifier or additive use); TEM (Technical or engineered material use); BIOL (Biological study); USES (Uses)
(**stabilizing** biol. material in collapsed matrix of a non-carbohydrate polymeric material)

IT 9002-89-5, Polyvinyl alcohol **9003-39-8**, Polyvinylpyrrolidone 25322-68-3, Polyethylene glycol
RL: BUU (Biological use, unclassified); POF (Polymer in formulation); TEM (Technical or engineered material use); BIOL (Biological study); USES (Uses)
(**stabilizing** biol. material in collapsed matrix of a non-carbohydrate polymeric material)

IT **69-65-8, Mannitol**
RL: BUU (Biological use, unclassified); MOA (Modifier or additive use); TEM (Technical or engineered material use); BIOL (Biological study); USES (Uses)
(**stabilizing** biol. material in collapsed matrix of a non-carbohydrate polymeric material)

RN 69-65-8 HCAPLUS
CN D-Mannitol (9CI) (CA INDEX NAME)

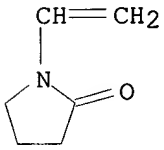
Absolute stereochemistry.



IT **9003-39-8**, Polyvinylpyrrolidone
RL: BUU (Biological use, unclassified); POF (Polymer in formulation); TEM (Technical or engineered material use); BIOL (Biological study); USES (Uses)
(**stabilizing** biol. material in collapsed matrix of a non-carbohydrate polymeric material)
RN 9003-39-8 HCAPLUS
CN 2-Pyrrolidinone, 1-ethenyl-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 88-12-0
CMF C6 H9 N O



L35 ANSWER 10 OF 10 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:664806 HCAPLUS
DOCUMENT NUMBER: 126:11459
TITLE: Optimizing the Lyophilization Cycle and the Consequences of Collapse on the Pharmaceutical Acceptability of Erwinia L-Asparaginase
AUTHOR(S): Adams, Gerald D. J.; Ramsay, J. Richard
CORPORATE SOURCE: Centre for Applied Microbiology and Research, Porton Down/Salisbury/Wiltshire, SP4 0JG, UK
SOURCE: J. Pharm. Sci. (1996), 85(12), 1301-1305
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The antileukemia enzyme, Erwinia L-asparaginase, occurs as a tetramer which can be dissocd. by the stresses of lyophilization into four subunits (subunit Mr 34 000 Da). Dissocn. can be reduced by adding protectants to the formulation to **stabilize** the biopolymer, while the product should dry to form a pharmaceutically elegant, shelf-stable cake which is readily sol. Using anal. ultracentrifugation, HPLC, and CD we have related structural dissocn. of the enzyme during lyophilization to biol. activity. Additives such as mannitol prevent ablation loss of vial contents and dry to form cosmetically elegant cakes but provide little biol. protection, since during freezing they crystallize and are removed from the prepn. Excipients persisting throughout the cycle in the amorphous state provide improved biol. protection, although high mol. wt. compds. such as Dextran (Mr 70 000 Da) are most effective only during product freezing or storage. Low mol. wt. sugars are protective

throughout the cycle although formulations contg. monosaccharides often exhibit low collapse temps. (Tc) measured using a freeze-drying microscope or glass transition temps. (Tg') measured by thermal anal., but these formulations distort as drying progresses to form a collapsed, cosmetically unacceptable cake, with reduced activity, poor **stability**, a high moisture content, and reduced soly. Collapse can be avoided by formulating with disaccharides, which display higher Tc temps. than monosaccharides, or drying below Tc. Dried samples which persist in the amorphous state can also collapse when stored above their solid-state collapse temps. when they decay at a faster rate than predicted by Arrhenius kinetics. The solid-state collapse temp. can be significantly decreased by the diffusion of moisture from the stopper into the dry product resulting in an increase in sample water content. Lyophilization cycle times can be reduced by analyzing collapse characteristics so that the relationship between product temp. and chamber pressure can be controlled so that drying rates can be optimized while ensuring that the product does not melt or collapse during sublimation.

CC 63-5 (Pharmaceuticals)

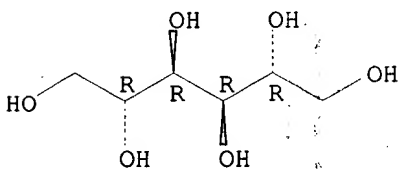
IT Erwinia
Freeze **drying**
Glass transition temperature
(optimizing the lyophilization cycle and the consequences of collapse on the pharmaceutical acceptability of Erwinia asparaginase)

IT 50-70-4, D-Glucitol, biological studies 50-99-7, D-Glucose, biological studies 57-50-1, Sucrose, biological studies 63-42-3 **69-65-8**, **Mannitol** 99-20-7, Trehalose **9003-39-8**, Pvp **9004-54-0**, **Dextran**, biological studies
RL: MOA (Modifier or additive use); PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(optimizing the lyophilization cycle and the consequences of collapse on the pharmaceutical acceptability of Erwinia asparaginase)

IT **69-65-8**, **Mannitol** **9003-39-8**, Pvp **9004-54-0**, **Dextran**, biological studies
RL: MOA (Modifier or additive use); PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(optimizing the lyophilization cycle and the consequences of collapse on the pharmaceutical acceptability of Erwinia asparaginase)

RN 69-65-8 HCAPLUS
CN D-Mannitol (9CI) (CA INDEX NAME)

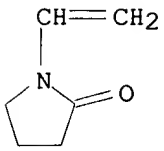
Absolute stereochemistry.



RN 9003-39-8 HCAPLUS
CN 2-Pyrrolidinone, 1-ethenyl-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 88-12-0
CMF C6 H9 N O



RN 9004-54-0 HCAPLUS
CN Dextran (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***